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BOOK 48
TAB# 1-70

LOW TAR AND DISEASE

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Lungenkrebs bei Angehörigen der Berufsgruppe „Chauffeur"

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Zusammenfassung

Unter 93 männlichen Bronchuskarzinompatienten der Berufsgruppe „Chauffeur" waren signifikant mehr Zigarettenraucher (97%) als unter den 153 Kontrollpersonen. Signifikante Unterschiede zwischen Patienten und (Kontrollen) bestehen bei: Jahre geraucht: 41,6 (34); Teerexpositionswert (TEW): 2569 (1966); Zahl der Exraucher: 37% (59%); Jahre Exraucher: 9,1 (16,6). Das Lungenkrebsrisiko der Zigarettenraucher nimmt mit steigendem TEW zu; signifikant ab TEW 1001; (= kritischer Bereich). Rauchende Chauffeure weisen nach Standardisierung von Berufsdauer und TEW gegenüber Rauchern der Gruppe „white collar" (bei denen eine berufliche Exposition – Inhalationsnoxen – anamnestisch ausgeschlossen werden konnte) ein etwas erhöhtes Lungenkrebsrisiko auf.

Key-Words: Lung cancer — Chauffeurs — Smooking habits — Lung cancer risk — Occupational exposure

Einleitung

In einer im ganzen Bundesgebiet durchgeführten Fallkontrollstudie über das Bronchuskarzinom und Tabakrauchen (*Kunze, Vutuc* 1978) haben wir von 1977 bis 1979 Daten von 1580 männlichen Lungenkrebspatienten und 3160 Kontrollpersonen erhoben. Die große Fallzahl ermöglicht eine Auswertung nach Berufsgruppen und damit eine Abschätzung des berufsbedingten Lungenkrebsrisikos im untersuchten Kollektiv. Über die Analyse der Berufsgruppe „Metallgewinnung und -verarbeitung" haben wir an dieser Stelle berichtet (*Vutuc, Kunze,* 1981). Die vorliegende Arbeit analysiert die Rauchgewohnheiten von Lungenkrebspatienten und Kontrollpersonen, die dem Berufsstand „Chauffeur" angehören. Weiters wird das berufsbedingte Lungenkrebsrisiko von zigarettenrauchenden Chauffeuren bestimmt. Das berufsbedingte Risiko konnte nur bei Zigarettenrauchern ermittelt werden, da eine entsprechende Auswertung für Niemalsraucher wegen zu kleiner Fallzahlen unter den Lungenkrebspatienten des Untersuchungs- und Vergleichskollektivs nicht durchgeführt werden konnte.

Patientengut und Methodik

Über Durchführung und Methodik der Fallkontrollstudie haben wir in der Analyse der Berufsgruppe „Metallgewinnung und -verarbeitung" ausführlich berichtet (*Vutuc, Kunze,* 1981); sie gelten analog für die vorliegende Arbeit.

Im ersten Untersuchungsabschnitt wurden aus dem Gesamtkollektiv (1580 Patienten, 3160 Kontrollpersonen) alle Personen mit dem Beruf „Chauffeur" ermittelt und deren Angaben über Alter, Dauer der Berufstätigkeit und Rauchstatus erhoben. Von den Zigarettenrauchern wurden Rauchdauer, Dauer der Abstinenz sowie alle jemals konsumierten Zigarettenmarken einschließlich jeweiliger Menge und Dauer des Konsums ermittelt.

Die angegebenen Zigarettensorten wurden entsprechend ihrem Teergehalt (Austria Tabakwerke 1977) einer von drei möglichen Markengruppen zugeordnet (*Kunze, Herberg, Vutuc* 1978). Gruppe I: < 15 mg/Zig.; Gruppe II: 15 bis 24 mg/Zig.; Gruppe III: > 24 mg/Zig. Aufgrund dieser Angaben wurde der Teerexpositionswert (= TEW) berechnet, indem die Summe der Produkte aus Zigarettenkonsum/Tag mal Konsumdauer/Jahre mal Gruppenfaktor (= 1, 2, 3) aller angegebenen Zigarettensorten gebildet wurde (*Vutuc* 1980).

Das Lungenkrebsrisiko gegenüber Niemalsrauchern (*Mantel-Haenszel* 1959) wurde berechnet für:

– Exraucher nach Jahren der Abstinenz,

– Zigarettenraucher in Relation zur Höhe der Teerexpositionswerte.

In einem zweiten Untersuchungsgang wurde das Berufsrisiko für Zigarettenraucher des Berufsstandes „Chauffeur" berechnet. Als Vergleichsgruppe wurden aus dem Gesamtkollektiv jene Personen ermittelt, bei denen anamnestisch eine Berufsexposition (Inhalationsnoxe) ausgeschlossen werden konnte (Gruppe „white collar"). Von den 784 Zigarettenrauchern (284 Patienten, 536 Kontrollpersonen) der 1091 Personen, die der Gruppe „white collar" angehörten, wurden die den Rauchern unter den Chauffeuren analogen Daten ausgewertet.

Das Lungenkrebsrisiko wurde für Zigarettenraucher der Berufsgruppe „Chauffeur" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teerexposition und gleicher Dauer der Berufstätigkeit berechnet.

Ergebnisse

a) Rauchgewohnheiten der „Chauffeure

Von den 1580 männlichen Patienten und 3160 Kontrollpersonen des Gesamtkollektivs wurden 93 Patienten und 153 Kontrollpersonen der Berufsgruppe „Chauffeure" zugeordnet.

82 (88%) der Patienten hatten einen Tumor der Gruppe Kreyberg I, 11 Patienten einen Tumor der Gruppe Kreyberg II.

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Tab. 1 Rauchstatus männlicher Bronchuskarzinompatienten (Gruppen Kreyberg I und Kreyberg II) und Kontrollpersonen, Berufsgruppe „Chauffeuer"

	alle Karzinome		Kreyberg I		Kreyberg II		Kontrollen	
	n	%	n	%	n	%	n	%
Zigaretten-raucher (Exraucher)	91+) (30)	98	81+) (30)	99	10 –	91	132 (78)	86
Niemals-raucher	2	2	1	1	1	9	21	14
Summe	93	100	82	100	11	100	153	100

+) $p < 1\%$

Der Rauchstatus der Patienten und Kontrollpersonen ist in Tab. 1 dargestellt (es handelt sich ausschießlich um Zigarettenraucher).

Karzinompatienten sowie Patienten mit einem Kreyberg I-Tumor waren signifikant häufiger (X^2 7,24, $p < 1\%$; X^2 8.42, $p < 1\%$) Zigarettenraucher als Kontrollpersonen.

Die zwei Patienten, die niemals geraucht haben, waren zum Zeitpunkt der Diagnose 46 und 71 Jahre alt und haben 23 und 40 Jahre als Chauffeur gearbeitet. Die Niemalsraucher unter den Kontrollpersonen waren durchschnittlich 63,9 Jahre (SF = 0,81) alt und waren durchschnittlich 28,2 Jahre (SF = 1,80) berufstätig.

In Tab. 2 sind die Durchschnittswerte für Alter zum Diagnosezeitpunkt, Dauer der Berufstätigkeit, Jahre geraucht und Teerexpositionswert für Patienten und Kontrollpersonen wiedergegeben.

Alle Patienten bzw. Patienten mit einem Kreyberg I-Tumor haben signifikant länger geraucht ($t = 4,82$, $p < 1\%$; $t = 4,65$, $p < 1\%$) und weisen einen signifikant höheren ($t = 3,43$, $p < 1\%$, $t = 3,51$, $p < 1\%$) Teerexpositionswert auf als die Kontrollpersonen.

Kontrollpersonen (78 = 59%) waren signifkant häufiger (X^2 15,78; $p < 1\%$) Exraucher als Karzinompatienten (30 = 37%). Mit durchschnittlich 16,6 Jahren (SF = 1,34) waren sie auch signifkant länger ($t = 3,09$, $p < 1\%$) abstinent als die Exraucher unter den Patienten, die seit durchschnittlich 9,1 Jahren (SF = 1,80) nicht mehr geraucht haben. In Tab. 3 ist das Lungenkrebsrisiko von Rauchern insgesamt, Jetztrauchern und Exrauchern in Relation zur Dauer der Abstinenz, verglichen zu den Niemalsrauchern, dargestellt.

Tab. 3 Männliche Zigarettenraucher, Berufsgruppe „Chauffeur", Lungenkrebsrisiko für Raucher insgesamt, Jetztraucher und Exraucher in Abhängigkeit zur Dauer der Abstinenz (Niemalsraucher: R = 1,0)

Dauer		Dauer der Abstinenz in Jahren					
Raucher insges.	Jetzt-Raucher	1–4	5–9	10–14	15–19	20–29	>30
7,24+)	11,86+)	12,00	3,50	1,75	2,33	2,10	1,97

+) $p < 1\%$

Das Lungenkrebsrisiko von Zigarettenrauchern in Abhängigkeit zur Höhe der Teerexposition gegenüber Niemalsrauchern ist in Tab. 4 wiedergegeben.

Das Lungenkrebsrisiko von Zigarettenrauchern nimmt bei einer Teerexposition von mehr als 1001 signifikant (X^2 5,37; $p < 5\%$) zu. Dies trifft für die Tumoren der Gruppe Kreyberg I (X^2 6,38; $p < 5\%$) zu; gegenüber den Kreyberg II-Tumoren ist die Zunahme des Risikos nicht signifikant.

b) Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Chauffeur" gegenüber Zigarettenrauchern der Gruppe „white collar"

In Tab. 5 sind die Durchschnittswerte für Alter, Jahre der Berufstätigkeit, Jahre geraucht und Teerexpositionswert der Kollektive „Chauffeur" und „white collar" wiedergegeben.

Die Zigarettenraucher der Gruppe „white collar" waren signifikant länger ($t = 4,41$, $p < 1\%$) berufstätig als Zigarettenraucher der Berufsgruppe „Chauffeur".

In Tab. 6 ist das Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Chauffeur" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teerexposition und gleicher Dauer der Berufstätigkeit wiedergegeben.

Diskussion

Die Ergebnisse spiegeln die ätiologische Bedeutung des Tabakkonsums für das Entstehen von Lungenkrebs wider. Mit der Ausnahme von zwei Personen waren alle Bronchuskarzinompatienten (98%) Zigarettenraucher. Verglichen mit den Rauchern in der Kontrollgruppe weisen sie ein extremes Konsumverhalten auf (signifikante Unterschiede bei Rauchdauer, Teerexpositionswert, Anteil der Exraucher und Dauer der Abstinenz). Diese Unterschiede

Tab. 2 Männliche Bronchuskarzinompatienten (Gruppe Kreyberg I und Kreyberg II) und Kontrollpersonen, Berufsgruppe „Chauffeur", Durchschnittswerte für Alter, Berufsdauer, Rauchdauer und Teerexpositionswert (1SF)

	alle Karzinome (n = 91)		Kreyberg I (n = 81)		Kreyberg II (n = 10)		Kontrollen (n = 132)	
Alter zum Diagnosezeitpunkt	62,2	(0,93)	63,4	(1,01)	62,0	(2,27)	63,2	(0,84)
Jahre berufstatig	27,7	(1,08)	26,0	(1,15)	24,8	(2,85)	26.2	(0,92)
Jahre geraucht	41,6+)	(1,13)	41,7+)	(1,24)	40,7	(2,26)	34,0	(1.04)
Teerexpositionswert	2569+)	(145)	2610+)	(158)	2240	(325)	1965	(106)

+) $p < 1\%$

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Tab. 4 Männliche Zigarettenraucher, Berufsgruppe „Chauffeur", Lungenkrebsrisiko in Relation zum Teerexpositionswert (Niemalsraucher: R = 1,0)

	Teerexposition						
	< 500	501—1000	1001—2000	2001—3000	3001—4000	4001—5000	> 5001
Alle Karzinome	1,50	2,19	6,20++)	8,93+)	12,41+)	31,50+)	15,75+)
Kreyberg I	3,00	2,63	11,45++)	16,80+)	17,18+)	36,00+)	31,50+)
Kreyberg II	–	1,25	0,95	1,05	7,64	–	–

+)$p < 1\%$; ++)$p < 5\%$

beziehen sich in erster Linie auf Patienten mit Tumoren der Gruppe Kreyberg I, die eine stark ausgeprägte ätiologische Beziehung zum Tabakkonsum (*Kreyberg* 1962) haben; entsprechend stellen sie im untersuchten Patientengut mit 88% den dominierenden Anteil der histologischen Typen. Diese Ergebnisse (Anteil der Kreyberg I-Tumoren, Anteil der Raucher, Rauchdauer und TEW) entsprechen unseren ersten Analysen der Studie nach Berufsgruppen (*Vutuc*, 1980).

Chauffeure, die Zigaretten rauchen, haben gegenüber Niemalsrauchern ein 7,5fach höheres Lungenkrebsrisiko. Durch die Berechnung des Teer-Expositionswertes ist eine quantitative Abstimmung des Risikos möglich. Mit steigendem

Tab. 5 Männliche Zigarettenraucher, Berufsgruppe „Chauffeur" und Gruppe „white collar", Durchschnittswerte für Alter, Berufsdauer, Jahre geraucht und Teerexpositionswert (1 SF). Karzinompatienten und Kontrollpersonen

	„Chauffeur" (n = 223)		„white collar" (n = 784)	
Alter	63,2	(0,62)	63,1	(0,37)
Jahre berufstätig	26,8	(0,70)	30,6+)	(0,42)
Jahre geraucht	37,1	(0,81)	35,9	(0,49)
Teerexpositionswert	2212	(89)	2049	(54)

+) $p < 1\%$

TEW nimmt das Risiko zu. Der „kritische Bereich" dieser Dosis-Wirkungsbeziehung, ab dem das Risiko signifikant ansteigt, liegt bei einem TEW von mehr als 1001. Diese Größenordnung für den „kritischen Bereich" konnte auch in früheren Untersuchungen bei Samples ohne Berücksichtigung der Berufszugehörigkeit (*Kunze, Vutuc* 1980a, *Vutuc, Kunze* 1981) und bei Metallarbeitern (*Vutuc, Kunze*, 1981) erhoben werden. Über die präventiv-medizinische Bedeutung des „kritischen Bereichs" haben wir an anderer Stelle ausführlich berichtet (*Kunze, Vutuc* 1980b). Gegenüber den Kreyberg II-Tumoren zeigt sich keine ausgeprägte Dosis-Wirkungsbeziehung; wegen der kleinen Fallzahlen kann diese jedoch nicht unbedingt ausgeschlossen werden.

Tab. 6 Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Chauffeur" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teerexposition und gleicher Dauer der Berufstätigkeit.

Jahre berufstätig	Teerexposition				
	501—1000	1001—2000	2001—3000	3001—4000	> 4001
11—20		< 2000 : 1,44	1,48		> 3000 : 2,50
21—30	4,50	2,14	1,04	1,02	3,86
31—40	1,40	1,33	1,60	1,23	3,25
41—50	1,33	4,44	2,75	–	–

Das Einstellen der Rauchgewohnheit führt im zeitlichen Verlauf zu einer raschen Abnahme des Erkrankungsrisiko

Zigarettenraucher der Berufsgruppe „Chauffeur" weisen gegenüber Rauchern der Gruppe „white collar", nach Standardisierung von Berufsdauer und TEW, ein erhöhtes Lungenkrebsrisiko auf; ein Hinweis auf eine mögliche berufsbedingte Risikokomponente im untersuchten Kollektiv. Ein etwas höheres als erwartetes Lungenkrebsrisiko konnten auch *Boucot* und Mitarb. (1972) bei den von ihnen untersuchten Chauffeuren nachweisen. Als Ursache wäre denkbar, daß Chauffeure an ihrem Arbeitsplatz vermehrt kanzerogenen Kohlenwasserstoffen (aus Autoabgassen) und Asbest (von Brems- und Kupplungsbelegen) ausgesetzt sein können. Eine qualitative und qantitative Aussage über diese Schadstoffbelastung ist im Rahmen der vorliegenden Untersuchung nicht möglich. Da die Risikozunahme zum Teil sehr gering ist, kann angenommen werden, daß berufsbedingte Schadstoffe eher die Wirkung des Tabakrauchs verstärken als eine direkte kausale Wirkung haben.

Selikoff und Mitarb. (1968) konnten bei Asbestarbeitern nachweisen, daß eine Zunahme des Lungenkrebsrisikos durch die Asbestexposition nur bei Rauchern feststellbar ist.

Aufgrund der dargestellten Ergebnisse ist die Noxe Tabak als ätiologischer Faktor für das Entstehen von Lungenkrebs bei den untersuchten Chauffeuren wesentlich höher einzuschätzen als eine mögliche berufsbedingte Exposition. Es wäre vorstellbar, daß das Tabakrauchen die Voraussetzung für die Wirkung der berufsbedingten Risikokomponente gebildet hat, in dem erst über eine Kontamination des inhalierten Tabakrauchs mit berufsbedingten Schadstoffen die folgewirksame Schadstoffbelastung ausgelöst wurde. Eine Überprüfung dieser Hypothese war wegen der zu geringen Zahl von Niemalsrauchern unter den Patienten des Untersuchungs- und Vergleichskollektivs nicht möglich.

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Lungenkrebs bei Angehörigen der Berufsgruppe „Metallgewinnung und -verarbeitung"

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Zusammenfassung

Unter 197 männlichen Bronchuskarzinompatienten der Berufsgruppe „Metallgewinnung und -verarbeitung" waren signifikant mehr Zigarettenraucher (97%) als unter den 311 Kontrollpersonen (78%). Patienten haben signifikant länger geraucht (41,6 Jahre) und weisen signifikant höhere Teer-Expositionswerte (TE = 2418) auf als Kontrollpersonen (36,5 Jahre, TE = 2108). Zigarettenraucher haben ein 8fach höheres Lungenkrebsrisiko als Niemalsraucher. Mit Zunahme des Teer-Expositionswertes steigt das Lungenkrebsrisiko der Zigarettenraucher signifikant an. Zigarettenraucher der Berufsgruppe „Metall" weisen nach Standardisierung von Dauer der Berufszugehörigkeit und Teer-Expositionswert gegenüber Rauchern der Gruppe „white collar" (bei denen eine berufliche Exposition –, Inhalationsnoxen – anamnestisch ausgeschlossen werden konnte) ein erhöhtes Lungenkrebsrisiko auf.

Key-Words: Lung cancer – Occupation mining and manufacturing of metall – Smoking habits – Lung cancer risk – Occupational exposure.

Einleitung

In einer überregional durchgeführten Fall-Kontroll-Studie (*Kunze, Vutuc,* 1978) haben wir in den Jahren 1977 bis 1979 Daten von 1 580 männlichen Bronchuskarzinompatienten und 3 160 Kontrollpersonen erhoben. Wegen der großen Fallzahl eignet sich dieses Datenmaterial besonders für die Auswertung nach Berufsgruppen. Diese Vorgangsweise ermöglicht eine Abschätzung der Bedeutung der beruflichen Exposition für das Lungenkrebsrisiko im untersuchten Kollektiv. In diesem Zusammenhang muß jedoch betont werden, daß die Beurteilung und Abschätzung einer berufsbedingten Beziehung meist sehr schwierig ist, da eine exakte ätiologische Abgrenzung der Synkarzinogenese und Kokarzinogenese beruflicher Noxen untereinander und vor allem mit der Noxe Zigarettenrauchen äußerst schwierig ist (*Schmähl,* 1977). Aus diesem Grund ist eine exakte Analyse der Rauchgewohnheiten und die quantitative Erfassung der Schadstoffbelastung der Zigarettenraucher notwendig. Aufgrund früherer Überlegungen (*Kunze,* 1975) haben wir zur Quantifizierung der Schadstoffexposition von Zigarettenrauchern ein Verfahren entwickelt (*Vutuc,* 1980), mit dem, unter Berücksichtigung der jeweiligen Menge, Konsumdauer und dem Schadstoffgehalt aller jemals gerauchten Zigaretten, eine Maßzahl für die individuelle Schadstoffbelastung (Teer-Expositionswert = TEW) des Zigarettenrauchers berechnet werden kann. Dieses Verfahren ermöglicht eine exakte Standardisierung der Rauchgewohnheit, wie sie bei der Bewertung beruflicher Expositionen unerläßlich ist.

Die vorliegende Arbeit analysiert die Rauchgewohnheiten von Lungenkrebspatienten und Kontrollpersonen der Berufsgruppe „Metallgewinnung und -verarbeitung". Weiters wird das berufsbedingte Lungenkrebsrisiko für Angehörige dieser Berufsgruppe untersucht. Für diesen Zweck wurden als Vergleichskollektiv jene Personen aus der Studie ausgewählt, bei denen eine berufliche Exposition (Inhalationsnoxen) anamnestisch ausgeschlossen werden konnte. In Anlehnung an den soziologischen Begriff wird diese Gruppe „white collar" genannt.

Die Ermittlung des berufsbedingten Risikos konnte nur bei den Zigarettenrauchern durchgeführt werden, da eine Auswertung für Niemalsraucher wegen zu kleiner Fallzahlen unter den Bronchuskarzinompatienten des Untersuchungs- und Vergleichskollektivs nicht durchgeführt werden konnte.

Patientengut und Methodik

In einer im gesamten Bundesgebiet (in 15 Zentren) durchgeführten Fall-Kontroll-Studie (*Kunze, Vutuc,* 1978) wurden in den Jahren 1977 bis 1979 Daten von insgesamt 1 580 männlichen Patienten mit einem histologisch und/oder zytologisch verifizierten Lungenkrebs erhoben. Die Erhebung erfolgte mittels eines standardisierten Fragebogens (*American Health Foundation,* 1976) zum Zeitpunkt der Verifizierung des Tumors.

Als Kontrollen wurden 3 160 altersmäßig entsprechende Personen befragt, die zum Zeitpunkt des Interviews nicht wegen einer tabakassoziierten Krankheit in ärztlicher Behandlung gestanden haben.

Im ersten Untersuchungsabschnitt wurden aus den Gesamtkollektiv alle Personen der Berufsgruppe „Metallgewinnung und -verarbeitung" ermittelt und deren Angaben ausgewertet.

Die verschiedenen histologischen Lungenkrebstypen wurden nach *Kreyberg* (1962) zusammengefaßt. Die Gruppe Kreyberg I, die mit dem Tabakkonsum in gesicherter ätiologischer Beziehung steht, umfaßt die histologischen Typen: Plattenepithel-, kleinzelliges-, großzelliges, undifferenziertes Karzinom sowie den Mischtyp Adeno-Kanthom. Die Gruppe Kreyberg II, bei der die ätiologische Bedeutung des Tabakkonsums noch nicht eindeutig gesichert ist, umfaßt das Adeno-, Alveolarzell- und Zylinderzellkarzinom.

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Bei den Zigarettenrauchern wurden neben dem gegenwärtigen Rauchstatus folgende weitere Aspekte berücksichtigt:

- Alter,
- Jahre berufstätig (Mindestdauer für die Zuordnung 7 Jahre),
- Gesamtrauchdauer in Jahren,
- Dauer der Abstinenz in Jahren und
- alle jemals gerauchten Zigarettenmarken einschließlich jeweiliger Menge und Dauer des Konsums.

Die angegebenen Zigarettenmarken wurden entsprechend ihrem Teergehalt (*Austria Tabakwerke*, 1977) einer von drei möglichen Markengruppen zugeordnet (*Kunze, Herberg, Vutuc*, 1978). Die Gruppe I umfaßt Zigaretten mit einem Teergehalt von unter 15 mg pro Zigarette, die Gruppe II mit einem Teergehalt von 15 bis 24 mg und die Gruppe III mit einem Teergehalt von über 24 mg pro Zigarette.

Der Teer-Expositionswert wurde nach folgender Formel (*Vutuc*, 1980) berechnet:

$$TEW = \sum_{i,j=1}^{n} (a_x b_x)_{ij} k_x + \sum_{i,j=i}^{n} (a_y b_y)_{ij} k_y + \sum_{i,j=1}^{n} (a_z b_z)_{ij} k_z$$

a_x, a_y, a_z = Zigarettenkonsum/Tag, Gruppen I, II, III

b_x, b_y, b_z = Zigarettenkonsumdauer/Jahre, Gruppen I, II, III

k_x, k_y, k_z = konstanter Faktor für Gruppen I, II, III (= 1, 2, 3)

Das Lungenkrebsrisiko (*Mantel, Haenszel*, 1959) wurde berechnet für:

- Raucher gegenüber Niemalsrauchern,
- Exraucher in Relation zur Dauer der Abstinenz gegenüber Niemalsrauchern und
- Raucher in Relation zur Höhe der Teer-Expositionswerte gegenüber Niemalsrauchern.

In einem zweiten Untersuchungsgang wurde das Berufsrisiko für Zigarettenraucher der Berufsgruppe „Metall" berechnet. Als Vergleichsgruppe wurden aus dem Gesamtkollektiv jene Personen ermittelt, bei denen anamnestisch eine Berufsexposition (Inhalationsnoxe) ausgeschlossen werden konnte (Gruppe „white collar"). Von den 248 (98%) Zigarettenrauchern unter den 252 Karzinompatienten sowie den 536 (64%) Zigarettenrauchern unter den 839 Kontrollpersonen, die der Gruppe „white collar" zugeordnet werden konnten, wurden folgende Angaben ausgewertet: Alter, Jahre berufstätig, Gesamtrauchdauer in Jahren und Teer-Expositionswert.

Das Lungenkrebsrisiko wurde berechnet für:

- Zigarettenraucher der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Dauer der Berufstätigkeit,
- Zigarettenraucher der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teer-Exposition und
- Zigarettenraucher der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teer-Exposition und gleicher Dauer der Berufstätigkeit.

Ergebnisse

a) Rauchgewohnheiten der Berufsgruppe „Metallgewinnung und -verarbeitung"

Von den insgesamt 1 580 befragten männlichen Patienten und 3 160 Kontrollpersonen wurden 197 Patienten und 311 Kontrollpersonen der Berufsgruppe „Metall" zugeordnet.

Von den 197 Patienten hatten 172 (87%) einen Tumor der Gruppe Kreyberg I, 25 Patienten einen Tumor der Gruppe Kreyberg II.

In Tab. 1 ist der Rauchstatus der Patienten und Kontrollpersonen dargestellt. Alle Raucher haben ausschließlich Zigaretten geraucht.

Karzinompatienten sowie Patienten mit einem Tumor der Gruppe Kreyberg I waren signifikant häufiger (x^2 32,01; $p < 1\%$ und x^2 31,11; $p < 1\%$) Zigarettenraucher als Kontrollpersonen.

Es bestehen keine signifikanten Unterschiede zwischen Rauchern und Niemalsrauchern im Alter und in der Dauer der Berufstätigkeit. Die Niemalsraucher unter den Patienten (6 Pers.) waren durchschnittlich 63,7 Jahre (SF = 2,17) alt und waren durchschnittlich 28,5 Jahre (SF = 1,51) berufstätig. Die 67 Kontrollpersonen, die niemals geraucht haben, waren durchschnittlich 63,4 Jahre alt (SF = 1,34) und durchschnittlich 30,8 Jahre (SF = 1,19) berufstätig.

In Tab. 2 sind das Durchschnittsalter zum Zeitpunkt der Diagnose, die durchschnittliche Dauer der Berufstätigkeit, die durchschnittliche Dauer der Rauchgewohnheit und der durchschnittliche Teer-Expositionswert für Patienten und Kontrollpersonen, die geraucht haben, wiedergegeben.

Tab. 1 Rauchstatus männlicher Bronchuskarzinompatienten (Gruppen Kreyberg I und Kreyberg II) und Kontrollpersonen, Berufsgruppe „Metallgewinnung und -verarbeitung"

	alle Karzinome		Kreyberg I		Kreyberg II		Kontrollen	
	n	%	n	%	n	%	n	%
Zigarettenraucher	191*	97	168*	98	23	92	244	78
(Exraucher)	(67)		(55)		(12)		(133)	
Niemalsraucher	6	3	4	2	2	8	67	22
Summe	197	100	172	100	25	100	311	100

* $p < 1\%$

Tab. 2 Männliche Bro winnung und -verarbei

Alter zum Diagnose-zeitpunkt	
Jahre berufstätig	
Jahre geraucht	
Teer-Expositionswert	

* $p < 1\%$

Tab. 3 Männliche Zig Jetztraucher und Exre

Raucher insgesamt	Jetzt-raucher
R = 8,74*	12,47*

* $p < 1\%$ ** p

Tab. 4 Männliche Zig Expositionswert (Nien

	<
alle Karzinome	3,
Kreyberg I	3,
Kreyberg II	2,

* $p < 1\%$

Alle Karzinompatie mor der Gruppe Kr 4,25; $p < 1\%$ und einen signifikant hö $p < 1\%$) Teer-Expo

Von den 191 Patier ten 67 (35%) zum Kreyberg I 55 (33% von 23. Von den in gruppe haben 133 (mehr geraucht. In Exraucher signifika den Patienten insge chern mit einem Tu $p < 1\%$).

Die Exraucher unter ten mit einem Tum durchschnittlich 11 (SF = 1,50) signifik 2,85; $p < 1\%$) abst trollpersonen (15,7 Tumor der Gruppe 14,6 Jahren (SF =

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Tab. 2 Männliche Bronchuskarzinompatienten (Gruppen Kreyberg I und Kreyberg II) und Kontrollpersonen, Berufsgruppe „Metallgewinnung und -verarbeitung", Durchschnittswerte für Alter, Berufsdauer, Rauchdauer und Teer-Expositionswert (1SF).

	alle Karzinome (n = 191)	Kreyberg I (n = 168)	Kreyberg II (n = 23)	Kontrollen (n = 244)
Alter zum Diagnosezeitpunkt	64,0 (0,68)	63,9 (0,72)	64,8 (1,91)	64,1 (0,64)
Jahre berufstätig	30,4 (0,78)	30,3 (0,84)	30,9 (1,50)	30,6 (0,65)
Jahre geraucht	41,6* (0,83)	42,3* (0,84)	36,3 (3,04)	36,5 (0,83)
Teer-Expositionswert	2418* (92, 91)	2485* (101, 81)	1929* (174, 59)	2108 (87, 40)

* $p < 1\%$

Tab. 3 Männliche Zigarettenraucher, Berufsgruppe „Metallgewinnung und -verarbeitung", Lungenkrebsrisiko für Raucher insgesamt, Jetztraucher und Exraucher in Abhängigkeit zur Dauer der Abstinenz (Niemalsraucher: R = 1,0)

		Dauer der Abstinenz in Jahren					
Raucher insgesamt	Jetztraucher	1–4	5–9	10–14	15–19	20–29	>30
R = 8,74*	12,47*	12,51*	4,19**	4,47**	5,08**	3,35	3,72

* $p < 1\%$ ** $p < 5\%$

Tab. 4 Männliche Zigarettenraucher, Berufsgruppe „Metallgewinnung und -verarbeitung". Lungenkrebsrisiko in Relation zum Teer-Expositionswert (Niemalsraucher: R = 1,0)

	Teer-Expositionswert						
	<500	501–1000	1001–2000	2001–3000	3001–4000	4001–5000	>5001
alle Karzinome	3,19	2,29	9,68*	11,64*	9,45*	8,77*	15,63*
Kreyberg I	3,59	2,58	12,73*	15,10*	12,88*	13,16*	23,45*
Kreyberg II	2,39	1,72	3,57	4,72	>3001 = 1,49		

* $p < 1\%$

Alle Karzinompatienten bzw. die Patienten mit einem Tumor der Gruppe Kreyberg I haben signifikant länger ($t = 4,25$; $p < 1\%$ und $t = 4,78$; $p < 1\%$) geraucht und weisen einen signifikant höheren ($t = 3,13$; $p < 1\%$ und $t = 2,79$; $p < 1\%$) Teer-Expositionswert auf als die Kontrollpersonen.

Von den 191 Patienten, die Zigaretten geraucht haben, waren 67 (35%) zum Zeitpunkt der Diagnose Exraucher; Kreyberg I 55 (33%) von 168 und Kreyberg II 12 (52%) von 23. Von den insgesamt 244 Rauchern in der Kontrollgruppe haben 133 (55%) zum Zeitpunkt der Diagnose nicht mehr geraucht. In der Kontrollgruppe war der Anteil der Exraucher signifikant größer als bei den Rauchern unter den Patienten insgesamt (x^2 15,51; $p < 1\%$) bzw. den Rauchern mit einem Tumor der Gruppe Kreyberg I (x^2 18,14; $p < 1\%$).

Die Exraucher unter allen Patienten bzw. unter den Patienten mit einem Tumor der Gruppe Kreyberg I waren mit durchschnittlich 11 Jahren (SF = 1,35) bzw. 10,2 Jahren (SF = 1,50) signifikant kürzer ($t = 2,61$; $p < 1\%$ und $t = 2,85$; $p < 1\%$) abstinent als die Exraucher unter den Kontrollpersonen (15,7 Jahre; SF = 1,11). Exraucher mit einem Tumor der Gruppe Kreyberg II haben seit durchschnittlich 4,6 Jahren (SF = 2,90) nicht mehr geraucht.

Das Lungenkrebsrisiko von Rauchern insgesamt, Jetztrauchern und Exrauchern, verglichen zu den Niemalsrauchern, ist in Tab. 3 dargestellt.

Das Lungenkrebsrisiko von Exrauchern nimmt mit der Dauer der Abstinenz ab, ohne jedoch das Erkrankungsrisiko von Niemalsrauchern zu erreichen.

Das Lungenkrebsrisiko von Zigarettenrauchern in Abhängigkeit zur Höhe der Teer-Exposition gegenüber Niemalsrauchern ist in Tab. 4 wiedergegeben.

Das Lungenkrebsrisiko von Zigarettenrauchern nimmt bei einer Teer-Exposition von mehr als 1001 signifikant (x^2 29,63; $p < 1\%$) zu. Dies trifft für die Tumoren der Gruppe Kreyberg I (x^2 29,21; $p < 1\%$) zu; gegenüber den Tumoren der Gruppe Kreyberg II ist die Zunahme des Erkrankungsrisikos nicht signifikant.

b) Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar"

Die Vergleichsdaten für die Berechnung des berufsbedingten Risikos von Zigarettenrauchern der Berufsgruppe „Metall" wurden einem Kollektiv von 748 Zigarettenrauchern

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Tab. 5 Männliche Bronchuskarzinompatienten und Kontrollpersonen, Berufsgruppe „Metallgewinnung und -verarbeitung" und Gruppe „white collar", Durchschnittswerte für Alter, Berufsdauer, Rauchdauer und Teer-Expositionswert (1SF)

	Metallgewinnung u. -verarbeitung		white collar	
	Karzinome (n = 191)	Kontrollen (n = 244)	Karzinome (n = 248)	Kontrollen (n = 536)
Alter	64,0 (0,68)	64,1 (0,64)	64,6 (0,57)	63,5 (0,46)
Jahre berufstätig	30,4 (0,78)	30,6 (0,65)	32,2 (0,63)	30,0 (0,54)
Jahre geraucht	41,6* (0,83)	36,5**(0,83)	42,3* (0,67)	32,9 (0,62)
Teer-Expositionswert	2418* (92, 91)	2108** (87, 40)	2649* (105, 84)	1771 (57, 91)

* $p < 1\%$, Fälle/Kontrollen ** $p < 1\%$, Kontrollen/Kontrollen

(248 Patienten, davon 215 mit einem Tumor der Gruppe Kreyberg I und 536 Kontrollpersonen) der Gruppe „white collar" entnommen (Tab. 5).

Im Kollektiv „white collar" haben Patienten signifikant länger ($t = 9{,}39$; $p < 1\%$) geraucht und weisen einen signifikant höheren ($t = 7{,}87$; $p < 1\%$) Teer-Expositionswert auf als Kontrollpersonen.

Signifikante Unterschiede zwischen beiden Kollektiven bestehen in den Parametern:

- *Jahre geraucht:*
  - Patienten „Metall : Kontrollen „white collar" ($t = 7{,}60$; $p < 1\%$);
  - Patienten „white collar" : Kontrollen „Metall" ($t = 5{,}50$; $p < 1\%$); und
  - Kontrollen „Metall : Kontrollen „white collar" ($t = 3{,}36$; $p < 1\%$).
- Teer-Expositionswert:
  - Patienten „Metall" : Kontrollen „white collar" ($t = 5{,}97$; $p < 1\%$);
  - Patienten „white collar" : Kontrollen „Metall" ($t = 3{,}92$; $p < 1\%$); und
  - Kontrollen „Metall" : Kontrollen „white collar" ($t = 2{,}90$; $p < 1\%$).

Tab. 6 Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metallgewinnung und -verarbeitung" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Dauer der Berufstätigkeit

	Jahre berufstätig				
	< 10	11–20	21–30	31–40	> 40
R	2,08	2,67*	1,75**	1,36	1,70

* $p < 1\%$ ** $< 5\%$

In Tab. 6 ist das Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Dauer der Berufstätigkeit wiedergegeben. Signifikante Unterschiede bestehen bei einer Berufsdauer von 11–20 Jahren (x^2 7,64; $p < 1\%$) und 21–30 Jahren (x^2 5,70; $p < 5\%$).

Die entsprechenden Werte bei gleicher Teer-Exposition sind in Tab. 7 dargestellt. Das Lungenkrebsrisiko der Berufsgruppe „Metall" ist im Bereich TEW 1001–2000 gegenüber der Gruppe „white collar" signifikant erhöht (x^2 8,88; $p < 1\%$).

Tab. 7 Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metallgewinnung und -verarbeitung" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teer-Exposition

	Teer-Expositionswert					
	501–1000	1001–2000	2001–3000	3001–4000	4001–5000	> 5001
R	1,61	1,88*	1,43	1,07	1,69	1,12

* $p < 1\%$

Tab. 8 Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metallgewinnung und -verarbeitung" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teer-Exposition und gleicher Dauer der Berufstätigkeit

Jahre berufstätig	Teer-Expositionswert					
	501–1000	1001–2000	2001–3000	3001–4000	4001–5000	> 5001
11–20	–	2,20	2,68	2,50	> 4001 = 2,00	
21–30	3,21	1,82	1,55	1,91	> 4001 = 1,02	
31–40	1,45	1,31	1,67	1,01	1,0	1,75
41–50	2,0	2,47	1,18	1,50	> 4001 = 1,14	

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Diskussion

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

In Tab. 8 ist das Lungenkrebsrisiko von Zigarettenrauchern der Berufsgruppe „Metall" gegenüber Zigarettenrauchern der Gruppe „white collar" bei gleicher Teer-Exposition und gleicher Dauer der Berufstätigkeit wiedergegeben.

Diskussion

Entsprechend der ätiologischen Bedeutung des Tabakkonsums für das Entstehen von Lungenkrebs handelt es sich bei den untersuchten Patienten der Berufsgruppe „Metall" fast ausschließlich um Zigarettenraucher; der Anteil ist signifikant größer als in der Kontrollgruppe. Gegenüber Niemalsrauchern weisen Zigarettenraucher ein 8fach höheres Lungenkrebsrisiko auf.

Das extreme Konsumverhalten der Patienten, verglichen mit den Kontrollpersonen, kommt in den signifikanten Unterschieden bei Rauchdauer und Teer-Expositionswert deutlich zum Ausdruck. Diese Unterschiede beziehen sich auf die Tumoren der Gruppe Kreyberg I, die unter den Rauchern mit 88% den dominierenden Anteil der histologischen Typen stellen. In einer früher durchgeführten Analyse nach Berufsgruppen (*Vutuc*, 1980) konnten wir unter den Patienten aller untersuchten Berufsgruppen entsprechend hohe Anteile von Kreyberg-I-Tumoren und, verglichen mit dem Kontrollkollektiv, extrem hohe Anteile von Rauchern mit längerer Dauer der Rauchgewohnheit und höheren Teer-Expositionswerten nachweisen.

Die Berechnung des Teer-Expositionswertes ermöglicht eine Quantifizierung der Schadstoffbelastung eines Zigarettenrauchers, da bei diesem Verfahren neben Menge und Dauer auch der Schadstoffgehalt der jeweils gerauchten Marke mitberücksichtigt wird. Das Lungenkrebsrisiko von Zigarettenrauchern nimmt gegenüber Niemalsrauchern mit steigendem TEW zu. Die Signifikanzschwelle liegt bei einem TEW von mehr als 1001. Dieser „kritische" Bereich der Teer-Exposition, ab dem das Risiko des Rauchers gegenüber einem Niemalsraucher signifikant ansteigt, entspricht den Ergebnissen früherer Untersuchungen (*Kunze, Vutuc*, 1980; *Vutuc* 1980; *Vutuc, Kunze*, im Druck), die bei männlichen und weiblichen Samples ohne Berücksichtigung der Berufszugehörigkeit erhoben wurden. Ein erhöhtes Erkrankungsrisiko besteht auch gegenüber den Tumoren der Gruppe Kreyberg II, ohne jedoch signifikante Werte zu erreichen.

Das Einstellen der Rauchgewohnheit führt im zeitlichen Verlauf zu einer Abnahme des Erkrankungsrisikos; es liegt jedoch auch nach langer Abstinenz über jenem von Niemalsrauchern.

Die Berechnung des Teer-Expositionswertes ermöglicht weiter die Standardisierung der Rauchgewohnheit, die wegen der großen Verbreitung des Zigarettenkonsums bei der Beurteilung einer beruflichen Exposition eine wichtige Voraussetzung darstellt. Da es sich bei den Patienten der untersuchten Kollektive fast ausschließlich um Zigarettenraucher („Metall" 97%; „white collar" 98%) gehandelt hat, wurde die Berechnung des berufsbedingten Risikos nur bei Rauchern durchgeführt.

Zigarettenraucher der Berufsgruppe „Metall" weisen bei gleicher Dauer der Berufstätigkeit bzw. gleichem TEW gegenüber Rauchern der Gruppe „white collar" ein jeweils erhöhtes Lungenkrebsrisiko auf. Das erhöhte Risiko besteht auch nach Standardisierung von Berufsdauer und TEW, ein Hinweis auf die berufsbedingte Ursache. Ob Faktoren aus dem Berufsbereich hier kausal wirken oder die Wirkung des Tabakrauchs verstärken, kann im Rahmen dieser Untersuchung nicht abgeschätzt werden. Die Berufsgruppe „Metall" umfaßt einen sehr großen Bereich verschiedener Berufe. Es kann daher angenommen werden, daß das dargestellte berufsbedingte Risiko durch einzelne Berufssparten bestimmt wird. So wurde z.B. bei Hochofenarbeitern (*Lloyd*, 1971) und bei Metallschmelzern (*U.S. Dept. Health, Education, Welfare*, 1973) ein erhöhtes Lungenkrebsrisiko nachgewiesen. In diesem Zusammenhang muß betont werden, daß die qualitative und quantitative Darstellung einzelner berufsbedingter Noxen sowie ihre zeitliche Einordnung, im Gegensatz zur Noxe Tabak, äußerst schwierig ist und die Präsenz dieser Noxen weitgehend durch die Zusammensetzung des Untersuchungskollektivs bestimmt wird. Dieser Umstand muß bei der Interpretation der Ergebnisse mitberücksichtigt werden, d.h., der Nachweis eines beruflichen Risikos bezieht sich in erster Linie auf das untersuchte Kollektiv, eine über den Rahmen des Untersuchungskollektivs hinausgehende Aussage ist im Gegensatz zum durch Zigarettenrauchen verursachten Risiko nur bedingt möglich.

Verglichen mit dem Erkrankungsrisiko der Raucher gegenüber den Niemalsrauchern der Berufsgruppe „Metall" ist die berufsbedingte Zunahme bei den Rauchern schwächer ausgeprägt. Entsprechend ist die Bedeutung der Noxe Tabak höher zu bewerten als jene der Berufsexposition. Dies zeigt sich auch darin, daß sich die Raucher beider Patientenkollektive bezüglich Alter, Dauer der Berufstätigkeit, Anteil der Patienten mit einem Tumor der Gruppe Kreyberg I („Metall" 88%; „white collar" 86,5%) sowie die Dauer der Rauchgewohnheit und Teer-Expositionswert nicht signifikant voneinander unterscheiden.

Auf die Darstellung von Interventionsmaßnahmen soll in dieser Arbeit nicht näher eingegangen werden; wir haben an anderer Stelle über Interventionsmöglichkeiten beim Bronchuskarzinom ausführlich berichtet (*Kunze, Vutuc*, 1980a). Es sei nur erwähnt, daß gerade bei Personen mit berufsbedingtem Lungenkrebsrisiko der Bekämpfung der Noxe Tabak, wegen der Schwierigkeiten bei der Erfassung beruflicher Noxen, besondere Bedeutung zukommt. Darüber hinaus sind natürlich alle Vorkehrungen zu treffen (nach dem jeweiligen Wissensstand und entsprechend den gesetzlichen Bestimmungen), die ein gesundheitliches Risiko der Arbeitnehmer in gefährdeten Berufen verhindern können.

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Vutuc, Ch., M. Kunze: Quantitative Bestimmung der Zigaretten-Kondensat-Exposition bei männlichen Bronchuskarzinom-Patienten der Altersgruppe 41 –50 Jahre. Öff. Gesundh.-Wesen im Druck

Univ.-Doz. Dr. med. Christian Vutuc, Univ.-Prof. Dr. med. Michael Kunze, Abteilung Sozialmedizin, Hygiene-Institut der Universität Wien, Kinderspitalgasse 15, A–1095 Wien

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BUCHBESPRECHUNGEN

Hahn, M.: Lebenskrise Krebs. Psychosoziale Aspekte der Betreuung Krebskranker. 1981. 160 S. (Schlütersche Verlagsanstalt, Hannover.) Geb. DM 39,80.

Es ist dankenswert, daß in dem vorliegenden Buch einmal sehr offen über die Krebserkrankung als sozialer Faktor gesprochen wird. Von der Verfasserin – aus langjähriger praktischer Erfahrung schöpfend – werden die Probleme aufgezeigt, die nicht nur von dem Erkrankten selbst, sondern auch von seiner Umwelt zu bewältigen sind. Da der Verlauf bzw. eine mögliche Heilung einer Krebserkrankung sehr wesentlich von den Beziehungen des Erkrankten zu seiner sozialen Umwelt abhängt, ist es sehr wichtig, daß die Verfasserin umfassend und mit Beispielen aus der Praxis aufzeigt, welche Faktoren im Umgang mit Krebskranken beachtet werden sollten.

Darüber hinaus gibt das Buch sehr genaue praktische Hinweise zu Fragen über soziale Hilfen, Renten, Wiedereingliederung etc. mit Angabe der Stellen, Organisationen, Verbände etc. Das Buch ist eine notwendige menschliche und praktische Information nicht nur für Assistenzberufe – auch für Ärzte, die mit Krebskranken zu tun haben.

Saalmann, Freiburg

White, K.L.: **Die Gesundheitsdienste:** Konzeptionen und Informationen für Planung und Management auf nationaler Ebene. Unter Mitarbeit v. Fachgelehrten. (Deutsche Zentrale für Volksgesundheitspflege-Schriftenreihe, Heft 32). 1977, 117 S., 33 Abb. (Weltgesundheitsorganisation, Genf.) Brosch.

Im Jahre 1977 gab die Weltgesundheitsorganisation die wohl umfassendste internationale Vergleichsstudie über das Gesundheitswesen heraus. Hieraus entstand eine Kurzfassung, die jetzt von der Deutschen Zentrale für Volksgesundheitspflege in deutscher Übersetzung vorgelegt wird. Themen sind internationale Probleme und Aufgaben der Gesundheitsdienste, Planung, Administration, Nutzung und Beurteilung von Gesundheitsdiensten sowie Ressourceneinsatz und internationale Zusammenarbeit.

Das Buch ist eine wertvolle Hilfe für Gesundheitspolitiker, Gesundheitsministerien, den öffentlichen Gesundheitsdienst und Forschungsinstitute, die sich mit Strukturfragen des Gesundheitswesens befassen.

F. Beske, Kiel

Brenner, W., H.J. Florian, E. Stollenz, H. Valentin (Hrsg.): **arbeitsmedizin aktuell.** Ein Loseblattwerk für die Praxis. Lieferung 5–7. 1980/81. (Gustav Fischer Verlag, Stuttgart.) Loseblattwerk mit Ordner.

Das Loseblattwerk, das sich bisher im täglichen Gebrauch gut bewährt hat, ist durch die 6. Lieferung (Nov. 80) und 7. Lieferung (Febr. 81) erweitert worden. So wurde die MAK-Liste ergänzt, die Angaben über die Informationszentren für Vergiftungen wurden aktualisiert. Neu aufgenommen wurde ein Abhandlung über Mutterschutz am Arbeitsplatz, Ausführungen über die Virushepatitis, Diagnostik, Therapie und der Siliko-Tuberkulose sowie der Silikose. Hinweise für Notfallsituationen am Arbeitsplatz wurden neu aufgenommen.

Weiterhin findet sich jetzt eine Übersicht über die Unfallverhütungsvorschriften wie auch eine Gebrauchsanweisung der ILO, der internationalen Klassifikation von Pneumokoniosen. Abhandlung über den Arbeitsaufenthalt im Ausland unter besonderen klimatischen Belastungen findet sich als weiterer Beitrag wie eine Abhandlung über physikalische Faktoren am Arbeitsplatz.

Insgesamt hat das hier vorliegende Werk weiter an Wert gewonnen. Alle Beiträge sind – wie die früheren – sorgfältig und überlegt niedergeschrieben worden.

Eine 8. Lieferung ist im Juni 1981 vorgesehen.

Deubel, Kiel

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Journal of Epidemiology and Community Health, 1982, **36**, 113–117

Cigarettes, lung cancer, and coronary heart disease: the effects of inhalation and tar yield

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From Papworth and Addenbrooke's Hospitals,[1] Cambridge, and the Department of Medical Statistics and Epidemiology,[2] London School of Hygiene and Tropical Medicine, London WC1E 7HT

SUMMARY Ten-year mortality rates for lung cancer and coronary heart disease have been related to cigarette smoking habits in 17 475 male civil servants aged 40–64 and in a sample of 8089 male British residents aged 35–69. Both diseases were more frequent in smokers. Lung cancer rates were higher overall for "non-inhalers", particularly in heavy smokers. Tar yield correlated with the risk of lung cancer in non-inhalers but less so in inhalers. Conversely, coronary deaths were more common among inhalers, and the effect of tar/nicotine yield (such as it was) was confined to inhalers. It appears that there are subtle interactions between the amount smoked, the tar/nicotine yield of the cigarette, and the style of smoking. Thus the effects of a change in cigarette characteristics are hard to predict, and they may be different for respiratory and cardiovascular disease.

Cigarette smoking is clearly associated with greatly enhanced risks of dying from coronary heart disease and lung cancer,[1–4] but less is known as to how tobacco smoke either causes or promotes these diseases. It seems likely that lung cancer results from a direct effect of smoke on airways,[5] while absorption from smoke of toxic constituents or metabolites contributes to coronary heart disease.[6] Fuller understanding is hampered by the chemical complexity of tobacco smoke, whose composition, moreover, undergoes intricate changes during inhalation into the lungs: the site and degree of absorption of each constituent are determined not only by its solubility but also by the manner in which the smoke is inhaled.[7,8] Little is known of the capacity of the lungs to detoxify tobacco smoke.

Thus the health consequences of smoking depend not only on the amount smoked but also on the composition of the smoke and the manner of smoking. All of these factors interact, so that, for example, a reduction in tar and nicotine yield may sometimes lead to deeper inhalation.[9] This suggests that at present we cannot predict the nett effect of changes in the characteristics of cigarettes.

To gain further insight into the relation of smoking to the development of lung cancer and coronary heart disease we have reviewed the mortality for these diseases among male civil servants in the Whitehall Study,[10] and among men in a sample of the British population surveyed in the US/UK/Norwegian Migrants Study.[11]

Methods

A total of 18 403 male civil servants in London, aged 40–64, took part in the Whitehall Study.[10] The British Council and the diplomatic service (873 men) had a different system for grading employment, and these men have therefore been excluded from the present analysis since this required adjustment for employment grade. Each completed a self-administered questionnaire that included details of men's current daily cigarette consumption, their answers to the question, "Do you inhale?" and their usual brand of cigarette (from which tar yield was assessed, using an unpublished list supplied by the Tobacco Research Council). Adequate smoking data were available from 17 475 men, among whom a total of 1657 deaths were identified over the next 10 years from the National Health Service Central Registry: 193 deaths were attributed to lung cancer (ICD 162·1, 8th revision) of which 143 occurred in cigarette smokers, and 704 to coronary heart disease (ICD 410–414), of which 407 were in cigarette smokers.

The data was cross-classified by age, employment grade, smoking factors (cigarettes a day, tar yield, and inhalation), and the analysis based on the method described by Nelder and Wedderburn.[12] This allowed "effects" of different factors—for example, tar yield—together with their interactions to be assessed while controlling concomitant variation attributable to other factors—for example, age and

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Table 1 *Number of men (%) in each age and cigarette smoking category (Whitehall Study)*

Age (years)	Non-smokers No (%)	Ex-smokers No (%)	Smokers: Inhalers No (%)	Smokers: Non-inhalers No (%)	Data incomplete No (%)	Total No (%)
40–49	1983 (27·2)	2514 (34·4)	2373 (32·5)	410 (5·6)	23 (0·3)	7 303 (100·0)
50–59	1535 (19·4)	2975 (37·6)	2592 (32·8)	779 (9·9)	21 (0·3)	7 902 (100·0)
60–64	359 (15·4)	888 (38·2)	761 (32·7)	306 (13·2)	11 (0·5)	2 325 (100·0)
All ages	3877 (22·1)	6377 (36·4)	5726 (32·7)	1495 (8·5)	55 (0·3)	17 530 (100·0)

Table 2 *Number of cigarette smokers according to daily consumption and tar yield showing inhalers and non-inhalers (%), (Whitehall Study)*

Tar yield (mg/cig)	Inhaling status	Daily consumption of cigarettes: 1–9 No	(%)	10–19 No	(%)	≥20 No	(%)
18–23	Inhaler	611	(63)	1379	(81)	1676	(85)
	Non-inhaler	356	(37)	322	(19)	296	(15)
24–32	Inhaler	185	(56)	450	(83)	554	(83)
	Non-inhaler	146	(44)	95	(17)	115	(17)
≥33	Inhaler	266	(80)	492	(87)	113	(82)
	Non-inhaler	67	(20)	74	(13)	24	(18)

employment grade. Mortality rates and χ^2 tests for significance were calculated using the fitted models, and standardisation for controlled factors was achieved by weighting the estimated model's coefficients. All rates have been standardised for employment grade, which strongly influenced smoking habits (including inhalation and tar yield) as well as having an independent effect on mortality. All the models fitted included age and employment grade together with all their interactions so that the analysis was equivalent to performing a stratified analysis with the tests of significance computed using the Mantel-Haenszel procedure.

In 1964–5 as part of the US/UK/Norwegian Migrants Study[11] we collected information on smoking habits from a sample of 8089 male UK residents aged 35–69; information on tar yield was unfortunately not recorded. Altogether 3707 were identified as smoking cigarettes only, and during the next 10 years 100 of these died from lung cancer and 247 from coronary heart disease.

Results

In table 1 men in the Whitehall Study are classified according to age and smoking habit. The proportion of cigarette smokers who said that they inhaled declined with age, from 85% at 40–49 down to 71% at 60–64 years. Table 2 shows that reported inhaling varied with amount smoked and with tar yield: it was less common in those who smoked under 10 cigarettes daily, unless their cigarettes were in the highest tar range. Older smokers tended to prefer a higher tar yield (table 3).

Table 3 *Numbers (%) in each age group smoking cigarettes of different tar yields (Whitehall Study)*

Age (years)	Tar yield (mg/cigarette): 18–23 No	(%)	24–32 No	(%)	≥33 No	(%)	Total No	(%)
40–49	1956	(70)	503	(18)	324	(12)	2783	(100)
50–59	2130	(63)	762	(23)	479	(14)	3371	(100)
60–64	554	(52)	280	(26)	233	(22)	1067	(100)

Lung cancer mortality was strongly and very significantly related to amount smoked ($p < 0{\cdot}01$) in both inhalers and "non-inhalers." This effect did not differ significantly between inhalers and non-inhalers. Overall, the mortality ratio for non-inhalers relative to inhalers was 1·25 ($p = 0{\cdot}3$). In table 4 the rates (adjusted for age and employment grade) are analysed by cigarette consumption and tar yield. Among inhalers the effect of tar yield was not large. It was not seen at all in the heaviest smokers, and overall it fell short of conventional significance. Tar yield was more important among non-inhalers ($p = 0{\cdot}03$), and thus the highest mortality from lung cancer was seen in non-inhalers who smoked high-tar cigarettes heavily.

Table 5 shows the lung cancer results from the migrants study. Among men smoking fewer than 20 cigarettes daily the rates are the same in inhalers and non-inhalers, whereas among heavier smokers they are higher in non-inhalers. This is the same pattern as in the Whitehall Study (last line of table 4).

Mortality from coronary heart disease in the Whitehall Study was higher in inhalers than non-inhalers (relative risk 1·30, $p = 0{\cdot}04$); but the

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Table 4 *Ten-year lung cancer mortality per hundred (and number of deaths) standardised for age and employment grade, according to cigarette consumption and tar yield (Whitehall Study)*

	Inhalers						Non-inhalers					
	1–9/d		10–19/d		≥20/d		1–9/d		10–19/d		≥20/d	
Tar (mg/cig)	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No
18–23	0·39	(2)	1·46	(19)	2·23	(35)	1·08	(4)	1·25	(5)	1·71	(7)
24–32	0·53	(1)	1·55	(8)	2·00	(13)	0·00	(0)	1·28	(2)	5·81	(9)
≥33	1·62	(7)	2·61	(20)	1·79	(3)	0·93	(1)	4·18	(5)	5·85	(2)
Total	0·87	(10)	1·79	(47)	2·13	(51)	0·75	(5)	1·76	(12)	3·01	(18)

Rate for life-long non-smokers of cigarettes = 0·20 (6).

Table 5 *Ten-year lung cancer mortality according to cigarette consumption (US/UK/Norwegian Migrants Study)*

	Inhalers			Non-inhalers			
	1–9/d	10–19/d	≥20/d	1–9/d	10–19/d	≥20/d	Incomplete information
No in group	365	1442	1283	133	222	150	112
No of deaths	6	38	35	3	8	9	1
Mortality (%) (age-adj)	1·64	2·69	3·05	1·64	2·70	5·07	—

Table 6 *Ten-year coronary heart disease mortality per hundred (and number of deaths) standardised for age and employment grade, according to cigarette consumption and tar yield (Whitehall Study)*

	Inhalers						Non-inhalers					
	1–9/d		10–19/d		≥20/d		1–9/d		10–19/d		≥20/d	
Tar (mg/cig)	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No
18–23	2·68	(14)	5·63	(71)	6·60	(101)	3·94	(14)	4·91	(17)	6·05	(20)
24–32	3·81	(7)	6·57	(30)	6·23	(36)	1·78	(3)	9·03	(10)	4·27	(6)
≥33	7·42	(23)	6·47	(37)	7·84	(10)	5·08	(4)	4·75	(4)	0·00	(0)
Total	4·29	(44)	5·98	(138)	6·56	(147)	3·48	(21)	5·73	(31)	5·18	(26)

Rate for life-long non-smokers of cigarettes = 2·75 (70).

relative risk was reduced to 1·16 ($p \simeq 0·25$) after adjusting for cigarette consumption and tar yield. Among inhalers the risk increased with the amount smoked ($p < 0·01$), but this effect was less evident in non-inhalers ($p \simeq 0·2$). In table 6 the rates (adjusted for age and employment grade) are analysed by cigarette consumption and tar yield. (Nicotine yield, which may be more relevant to cardiovascular risk, was strongly correlated with tar yield). Among inhalers there was a tendency ($p = 0·07$) for the highest rates to be seen in those smoking cigarettes with the highest tar yield. Among non-inhalers there was no clear pattern. This trend is illustrated by the relative risks for inhalers *v* non-inhalers at different levels of tar yield: 1·03 at 18–23 mg, 1·19 at 24–32 mg, and 1·91 in the highest tar group. This contrasts with what was found for lung cancer, where the effect of tar yield was stronger among non-inhalers than inhalers.

In the US/UK/Norwegian Migrants Study the general trend was similar, mortality from coronary heart disease being 1·25 times higher in inhalers than non-inhalers, after adjusting for age and daily cigarettes.

Discussion

In common with previous studies we found among cigarette smokers a much increased risk of lung cancer and fatal coronary heart disease. This risk was dose-related, except perhaps for coronary heart disease in non-inhalers. Our observations point also to a further dimension in the hazards associated with smoking—namely, the manner of smoking seems to relate differently to the risks of lung cancer on the one hand and of coronary heart disease on the other.

A greater risk of coronary heart disease among smokers who inhale is well recognised[1 13] It is usually thought that the same should apply to the risk of lung cancer, and the results of Hammond's large American study[4] supported this view. In the British doctors study, however, non-inhalers taken as a whole had a higher lung cancer mortality than inhalers.[4] This effect arose from a considerable excess among non-inhalers smoking 25 or more cigarettes daily. Our results, from both the Whitehall Study and the US/UK/Norwegian Migrants Study (table 5), support the reality of this unexpected

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phenomenon. There is a consistency between these three studies, and perhaps the different finding in Hammond's study came from a failure to take simultaneous account of the amount smoked.

The occurrence of a risk of lung cancer in smokers who deny inhaling shows that rhe answers to this question are unreliable, since the excess risk must imply exposure of bronchi to smoke. In fact, Wald and his colleagues[14] found that carboxyhaemoglobin levels in self-described non-inhalers were closer to those of inhalers than to those of non-smokers. Habits, moreover, may change, through disease, through a change in the type of cigarette, or for other reasons. The different associations with risk nevertheless show that the question on inhaling serves to discriminate two extremes of smoking behaviour. Other things being equal, the risk of coronary heart disease was higher in those reporting inhalation, whereas the risk of lung cancer was lower, at least for older and heavier smokers. The yield of tar affected the risk of lung cancer more among non-inhalers, whereas an effect of tar (or nicotine) on coronary heart disease was seen mainly among inhalers.

The average tar yield of cigarettes has been falling for many years.[15,16] This is due partly to manufacturing changes, partly to a growing preference for filtered cigarettes, and partly to the death of older smokers (who prefer a higher tar yield, table 3). Most cigarettes on sale today yield less tar than the lowest category in our initial survey (18–23 mg), which was conducted 10–12 years ago. Differences within the much lower current range may not have the same influence on disease as those which we observed between the higher levels. The case for advocating a reduction from middle to low yield of tar rests on extrapolation from the differences observed between smokers of high (or very high) and middle yields. Our findings (table 4) give little support for such extrapolation. Further analysis of smokers in the lowest tar category (18–23 mg) showed that although cigarette consumption was still a strong risk factor for both lung cancer and coronary heart disease ($p < 0.01$), there were no differences between inhalers and non-inhalers for these causes of death.

The results for coronary heart disease imply that the relationship to smoking depends on the absorption of smoke products. Unfortunately, it is not known which particular factor is to blame. Full inhalation much enhances the alveolar absorption of both soluble and less soluble gaseous components, including nicotine.[9]

The results for lung cancer are less readily explained. Possibly during full inhalation the smoker passes a concentrated bolus of smoke swiftly past the tumorigenic zone: by the time he exhales, the gases have been largely absorbed and most of the particulate matter has been deposited in the depths of the lungs, whence it is cleared by macrophages or by ciliary action. The situation is different for the non-inhaler—that is, the unwitting inhaler. If his inhalation occurs later in inspiration then the concentration of smoke in the "dead space" air might be higher than for the bolus inhaler: and it is this dead space fraction of the tidal volume that remains longest in contact with the main bronchi. Alternatively, his inhalation may be spread more evenly throughout inspiration with the same effect.

Regardless of the explanation of the phenomenon, the important lesson is that the risks of smoking depend not only on what is smoked but on how it is smoked. The interactions are subtle, incompletely understood, and hence not predictable. Smokers changing to a product yielding less tar and nicotine may tend to compensate for the fall in nicotine by inhaling more deeply.[9] This might be additionally beneficial for the lung cancer risk, but it could possibly increase the larger danger of fatal coronary heart disease. More circumspection is needed in advocating such a change, with more research into its long-term influence on the absorption of smoke products.

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8

Epidemiology of Polycyclic Hydrocarbons: Quantifying the Cancer Risk from Cigarette Smoking and Air Pollution

MALCOLM C. PIKE AND BRIAN E. HENDERSON

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I. INTRODUCTION

A number of polycyclic aromatic hydrocarbons (PAH) cause malignant tumors in experimental animals, and the evidence that they can and do cause (i.e., increase the incidence of) cancer in man has been best documented by epidemiologic studies showing increased rates of cancer in men exposed to PAH either through occupation or through cigarette smoking. These occupational studies, and many other aspects of PAH-associated human cancer, are discussed at length in Volume 3 of the "International Agency for Cancer Research Mono-

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graphs on the Evaluation of Carcinogenic Risk of Chemicals to Man" (*24*) and reviewed again in "Supplement 1 of the Monographs" (*25*). The supplement summarizes the current position as follows: "Occupational exposure to coal-soot, coal-tar and pitch, coal tar fumes and some impure mineral oils causes cancer of several sites, including skin, lung, bladder, and gastrointestinal tract." Interested readers are directed to these reports for details and references to original papers. The occupational studies are also discussed briefly in an earlier chapter by Guerin (*13*) and his Table VII gives many literature references. We will concern ourselves here only with studies of those occupational exposures that appear to have some relevance to the cancer risk of the general population.

The general population is exposed to PAH through air pollution, food, and water. Except for special occupational groups, however, the major human cancer risk associated with PAH is undoubtedly that caused by cigarette smoking. Only by understanding and taking account of the very strong relationship between cigarette smoking and lung cancer can one have any hope of quantifying the risk from PAH exposure from air pollution, and we will therefore begin this chapter by discussing what we know about the quantitative relationship between cigarette smoking and lung cancer. On this basis we will then discuss the potential lung cancer risk from air pollution. Compared to the risk of lung cancer, other risks from air pollution must be considered negligible—this is clear from consideration of the carcinogenic effects of cigarette smoking (*4, 9*)—and we will not discuss these other potential effects further.

The potential risk associated with PAH consumption in food and water is extremely difficult to study epidemiologically and probably for this reason has received little attention in the epidemiologic literature. What is known about the epidemiology of stomach and colorectal cancer does not suggest that PAH consumption in food is a major cause of cancer at either site (*16, 21*), and no studies have been reported even correlating PAH consumption with such cancers. It would be surprising if no risk at all was associated with oral consumption of PAH, but prediction of such effects will have to be made on the basis of animal experiments. However, it should be noted that by smoking 20 cigarettes a day, an amount associated with a substantial risk of lung cancer, one is breathing in less than 1 μg benzo[*a*]pyrene (BP), and this amount certainly does not exceed by much the amounts of BP consumed in food (*1*).

II. CIGARETTE SMOKING AND LUNG CANCER

The epidemiologic evidence implicating cigarette smoking as the major cause of lung cancer is overwhelming. Those still interested in pursuing the evidence are referred to an earlier chapter by Hoffman *et al.* (*23*), where the evidence is

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briefly discussed, and to the latest report of the Surgeon General "Smoking and Health" (*4*). We wish to concentrate on what these studies have to teach us both about what precautions we need to take in evaluating the lung cancer risk from air pollution and about quantitating this risk.

We can summarize much of what is known about the epidemiology of lung cancer in three fairly simple equations.

Among "never-smokers" the lung cancer incidence rate at age t (i.e., the probability of being diagnosed with lung cancer within the next year given that one is alive without a diagnosis of lung cancer at age t) may be written (*5*)

$$I_0(t) = a(t - 2)^{4.5} \tag{1}$$

where the subscript 0 signifies zero cigarettes per day, and the constant a is roughly 0.2×10^{-11}. For an American smoker of c cigarettes per day starting at age w the lung cancer rate at age t may be written

$$I_c(t) = a(t-2)^{4.5} + 2.5ac(t-w-2)^{4.5} \tag{2}$$

Equation (1) for never-smokers describes the age incidence curve in the mathematical form that holds for many non-hormone-dependent epithelial tumors (*3*), and Eq. (2) adds a cancer incidence of the same mathematical form arising from smoking. The cancer incidence curve arising from smoking only begins of course after smoking has begun, and the term $(t-w-2)$ is the duration of smoking to age t minus a minimum "latent period" of 2 years.

For a smoker of c cigarettes per day starting at age w and stopping at age s, the lung cancer incidence at age t may be written

$$I_{cs}(t) = a(t-2)^{4.5} + 2.5ac(s-w)^{4.5} \tag{3}$$

for t greater than $(s + 2)$ with the obvious modifications for t between s and $(s + 2)$. Equation (3) thus assumes that the *added* incidence from cigarette smoking remains constant at the level it had reached when smoking stopped (*32*).

Equations (1)–(3) are not meant to imply that lung cancers "caused" by smoking are separable (even conceptually) from tumors not so caused, nor that smoking affects only one "stage" of the lung cancer process (*32*), but rather, as we stated above, the formulas are to be regarded simply as a mathematical shorthand summarizing much of our knowledge of lung cancer epidemiology.

The major features of lung cancer epidemiology described by Eqs. (1–3) are illustrated in Tables I–III. The facts are as follows:

1. At any given age the lung cancer rate increases in direct proportion to the number of cigarettes smoked per day (Table I).

2. The relative risk at any given level of number of cigarettes smoked per day increases with age (Table IB).

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TABLE I

Calculated Lung Cancer Incidence in Continuing Cigarette Smokers Starting to Smoke at Age 20

No. cigarettes per day	Age 40	50	60	70
	A. Incidence/100,000			
0	2.6	7.4	17.2	35.3
20	7.0	39.9	145.8	403.0
40	11.5	72.4	274.3	770.8
	B. Relative risks compared to never-smoker			
20	2.7	5.4	8.5	11.4
40	4.5	9.8	15.9	21.9

3. The risks associated with smoking are very large. A one-pack-a-day smoker has, at age 60, some 8.5 times a never-smoker's incidence of lung cancer (Table IB).

4. The risks associated with smoking depend strongly on age at starting to smoke, i.e., on duration of exposure (Table II). The lung cancer rate of a one-pack-a-day smoker at age 60 is increased roughly 66% by starting smoking 5 years earlier (cf. starting at age 15 to starting at age 20 or starting at age 20 to starting at age 25 in Table IIB). Compared to starting smoking at age 20, each year earlier starting increases the lung cancer rate by roughly 12% and each year later starting decreases the rate by roughly the same amount.

5. Stopping smoking (i.e., becoming an exsmoker) at any age has a marked beneficial effect on lung cancer incidence rates (Table III). The lung cancer rate

TABLE II

Calculated Lung Cancer Incidence in Continuing Cigarette Smokers of 20 Cigarettes per Day by Age at Start of Smoking

Age at start of smoking	Age 40	50	60	70
	A. Incidence/100,000			
15	16.0	75.5	241.4	609.7
20	7.0	39.9	145.8	403.0
25	3.6	20.8	85.4	259.4
	B. Relative risk compared to start at age 20			
15	2.28	1.89	1.66	1.51
25	0.51	0.52	0.59	0.64

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among persons who have stopped for 10 years is only some 40–50% of the rate they would have been subject to if they had continued to smoke the same number of cigarettes per day (first diagonal in Table IIIB). Similarly, the lung cancer rate among persons who have stopped for 20 years is less than 20% of the rate in continuing smokers, and among persons who have stopped for 30 years the lung cancer rate is only some 12% of the rate in persons continuing to smoke. Stopping after only 10 years smoking leaves the exsmoker with a lung cancer rate less than 5% greater than the rate in a never-smoker 20 years later at age 50 (Table IIIC). However, stopping after 30 years of smoking, at age 50, leaves the exsmoker with a lung cancer rate more than double the never-smokers rate 20 years later at age 70 (Table IIIC), but only one-fifth the rate of the continuing smoker (Table IIIB).

The figures shown in *Tables I–III* are in excellent agreement with the large cohort studies of cigarette smoking and lung cancer (*4, 5, 9, 10*). Even these large cohort studies cannot, however, investigate all facets of the model represented by Eqs. (1)–(3), but it is very reasonable to assume that use of these formulas to predict lung cancer risk under differing circumstances is unlikely to lead us far astray.

TABLE III

Calculated Lung Cancer Incidence in Never-Smokers and Smokers of 20 Cigarettes per Day Starting to Smoke at Age 20 by Age at Stopping

No. cigarettes per day	Age at stopping	No. years smoked	Age			
			40	50	60	70
		A. Incidence/100,000				
0	—	—	2.6	7.4	17.2	35.3
20	—	—	7.0	39.9	145.8	403.0
20	30	10	2.9	7.7	17.6	35.6
20	40	20	—	14.5	24.4	42.4
20	50	30	—	—	61.6	79.6
20	60	40	—	—	—	197.2
		B. Relative risks compared to not stopping				
20	30	10	0.41	0.19	0.12	0.09
20	40	20	—	0.36	0.17	0.11
20	50	30	—	—	0.42	0.20
20	60	40	—	—	—	0.49
		C. Relative risks compared to nonsmokers				
20	—	—	2.7	5.4	8.5	11.4
20	30	10	1.12	1.04	1.02	1.01
20	40	20	—	2.0	1.4	1.2
20	50	30	—	—	3.6	2.3
20	60	40	—	—	—	5.6

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In the first volume of this work, Hoffman *et al. (23)* discussed various methods, such as use of filter tips or reconstituted tobacco, for reducing the "tar" content of cigarettes. They pointed out that the major carcinogenic activity of cigarette smoke resides in the particulate phase of the smoke (the tar), and that there is good experimental evidence that cigarettes with lower tar yields are less tumorigenic to both the larynx of hamsters and mouse skin. One would therefore naturally assume that, at the same cigarette consumption, users of "low tar" cigarettes will have lower lung cancer rates, unless the mode of smoking (i.e., number of puffs per cigarette and depth of inhaling) is markedly increased in low tar smokers. This has been borne out in all the epidemiologic studies that have investigated this question. A number of case-control studies have found that people who smoke filter tip cigarettes do have lower lung cancer rates compared to smokers of plain cigarettes at the same consumption level (*2*, *40*, *41*), and Hammond *et al. (20)* found in the American Cancer Society (ACS) cohort study that persons smoking low-tar cigarettes did have a reduced risk of lung cancer when compared to high-tar cigarette smokers (matched, of course, for numbers of cigarettes smoked per day).

Table IV shows the results of the ACS study: the lung cancer mortality ratios are clearly not decreased in proportion to tar content in men, but they are nearly so in women. This latter suggests that the added lung cancer risk is close to being simply proportional to tar content, with the failure to find a proportional reduction in men arising from the low-tar male smokers having switched from high-tar cigarettes. As Hammond *et al. (20)* explain

> Cigarettes with reduced tar and nicotine were not introduced until the mid 1950's. . . . Almost all of the male cigarette smokers and the great majority of the female cigarette smokers in our study began smoking cigarettes long before that date. Therefore the subjects classified here as low [tar] cigarette smokers were, with few exceptions, persons who smoked high [tar] or medium [tar] cigarettes for many years and then switched to low [tar] cigarettes.

TABLE IV

Lung Cancer Mortality Ratios for High, Medium, and Low "Tar" Cigarette Smokers for the Period 1960–1972[a]

"Tar" content (mg/cig)[b]	Mortality ratios[c]	
	Males	Females
High (30)	1.0	1.0
Medium (22.5)	0.95	0.80
Low (15)	0.81	0.60

[a] From Hammond *et al.* (*20*).
[b] Estimated from Hammond *et al.* (*20*).
[c] Estimated from Fig. 7 of Hammond *et al.* (*20*).

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Differing tar content of cigarettes may be incorporated into Eqs. (2) and (3) by expressing cigarette consumption in terms of equivalent numbers of "standard" cigarettes. The formulas as written apply to cigarettes with a tar content of some 30–35 mg and to "average" American smoking practices. Smoking practice is, of course, not only a function of depth of inhalation, but also of number of puffs per cigarette and butt length. A most notable example of this is seen when the results of British and American studies on lung cancer are compared: in Britain the lung cancer risk associated with smoking a given number of cigarettes is almost twice as high as in the United States (*17, 38*), and this is probably mainly attributable to the British mode of smoking cigarettes. In particular, it may be noted that around 1960 the average butt length in Britain was only 19 mm compared to 31 mm in the United States (*6, 17*). These extra 12 mm at the "end" of the cigarette will contribute a substantial amount of tar since the amount of tar derived from equal-sized puffs increases rapidly as the cigarette becomes shorter (*12, 33*).

In quantitating the effects of industrial exposure to PAH in air, it is necessary to have a cigarette–lung cancer model that can accommodate a change in cigarette consumption (or equivalently, a change in tar levels). In the "spirit" of Eq. (3) we may write, for a smoker starting smoking c_1 cigarettes per day at age w_1 and then changing to c_2 cigarettes per day at age w_2, the lung cancer incidence at age t as

$$I_{c_1,c_2}(t) = a(t-2)^{4.5} + 2.5ac_1(w_2-w_1)^{4.5} + 2.5ac_2[(t-w_1-2)^{4.5} - (w_2-w_1)^{4.5}] \quad (4)$$

for t greater than $(w_2 + 2)$ with the obvious modifications for t between w_2 and $(w_2 + 2)$. Equation (3) is a special case of Eq. (4) with $c_2 = 0$. Equation (4) assumes that on changing the number of cigarettes per day the *increment* in lung cancer incidence from there on will be as if the new level of cigarette smoking had been adopted when smoking began.

Equation (4) almost certainly gives too much emphasis to the new smoking level. An alternative is

$$I^*_{c_1,c_2}(t) = a(t-2)^{4.5} + 2.5ac_2(t-w_2+t'-w_1-2)^{4.5} \quad (5)$$

for t greater than w_2, where

$$t' = [c_1(w_2-w_1)^{4.5}/c_2]^{1/4.5}$$

Equation (5) assumes that on changing the number of cigarettes per day from c_1 to c_2 at w_2 the age incidence curve moves over to that applicable to c_2 at the time (duration of smoking) point which makes the incidence on the c_2 curve equal to the incidence on the c_1 curve at w_2. Equation (5) probably gives too little emphasis to the new smoking level. [Note that if c_2 is greater than c_1 then rates calculated from Eq. (4) will always be higher than rates calculated from Eq. (5).]

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III. AIR POLLUTION AND LUNG CANCER

The occurrence of PAH and particularly BP in "urban" air was reviewed in earlier chapters (*1, 13*). Large-scale studies of BP in the air of the United States were conducted between 1958 and 1959 by Sawicki *et al, (37)*. At that time the range of BP values in urban air was from less than 1 ng/m³ to around 60 ng/m³: some representative values are given in Table V, and the median concentration was roughly 6 ng/m³. In contrast, BP concentrations in air at nonurban sites were almost always less than 1 ng/m³ with a median concentration of 0.4 ng/m³. Since that time BP concentrations have decreased, and by 1969 the median BP concentration in air at urban sites was down to less than 2 ng/m³ (*31*). However, some cities were still experiencing average annual levels of BP approaching 10 ng/m³.

Not surprisingly, BP is neither a perfect indicator of PAH in the air nor of its carcinogenicity. Sawicki (*36*) reported that the amount of BP in the air is highly correlated with total PAH, but this will not be true if the source of the pollution is very different (e.g., automobile exhaust in one area and coal burning in another), and in this situation BP may be even a less constant proportion of the carcinogenicity of the total air pollution tar (*11, 22*). The latter point is particularly important since BP constitutes only a small proportion of the carcinogenicity of both air pollution and cigarette tar in experimental situations (*11, 27, 39*). Nevertheless, BP is a widely available indicator of PAH and is the best indicator available of the potential carcinogenicity of general air pollution.

A man breathes some 15 m³ of air per day so that living in air containing BP at a concentration of 10 ng/m³ one would breathe in some 150 ng BP per day. This

TABLE V

Average Benzo[*a*]pyrene (BP) Concentrations in the Air of U.S. Cities for the Period July, 1958 to June, 1959[a]

City	Average BP concentration (ng/m³)
Atlanta	6
Birmingham	--
Cincinnati	11
Detroit	15
Los Angeles	3
Nashville	18
New Orleans	4
Philadelphia	8
San Francisco	2

[a] From Sawicki *et al.* (*37*).

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is roughly the equivalent of 5 old-style cigarettes (*23*). It is, therefore, not unreasonable to assume that this level of pollution, which was very common only 20 years ago, may cause a significant amount of lung cancer. One does not breathe as if one were smoking, however, and it is therefore important to study the problem directly. This proves to be difficult to do satisfactorily, since any such investigation has to be especially careful to ensure that any observed effect is not attributable to differences in smoking habits between high- and low-pollution areas. As we have seen, the lung cancer rate is affected not only by the number of cigarettes smoked, but by the tar content of the cigarette, by how far down the cigarette is smoked, and by the age at starting to smoke; all these aspects of smoking habits have to be considered.

Since accurately allowing for all these smoking factors is clearly not possible, we must look either for an "extreme" situation in which minor smoking habit differences can be ignored or for data on lung cancer rates in nonsmokers in areas subject to different levels of pollution. Men employed in certain occupations involved in the making of coal gas or coke are exposed intermittently to levels of BP in air up to 16,000 ng/m^3 (*26*); such workers clearly provide us with an opportunity to study lung cancer effects in an extreme situation. We will discuss those studies of occupational exposure next and then finally compare the results suggested by these studies to the observed "urban/rural" ratio of lung cancer rates in never-smokers.

A. British Gasworkers

In a prospective study, Doll *et al.* (*7,8*) followed a cohort of carbonization workers in a number of British gasworks for up to 12 years. These carbonization workers were exposed to an estimated average air exposure of 3,000 ng/m^3 BP during an 8-hour shift (*28*); and these "exposed" workers experienced a 142% increase in lung cancer mortality rates when compared to the rates in their "unexposed" workmates (Table VI). (Note that 75% of newly diagnosed lung cancer cases are dead within a year and 90% within 3 years, so that distinguishing between incidence and mortality is therefore not particularly critical.)

Although the smoking habits of only some 10% of the cohort were ascertained by Doll and his colleagues (*7*), it is clear that the exposed and unexposed workers had very similar smoking habits with an average current cigarette consumption of just over 10 cigarettes per day (Table VI). It is reasonable therefore to assign the excess lung cancer in the exposed group to their working conditions and specifically to the air pollution to which they were exposed.

For those years during which the worker was actually exposed, his average daily exposure to BP expressed in air pollution equivalent terms, i.e., as if he had breathed such air throughout each day, would be

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TABLE VI

Smoking Habits and Lung Cancer Mortality Rate of British Gasworkers

Population	Nonsmokers (%)	Exsmokers (%)	Continuing smokers (%)					Lung cancer death rate[a]
			Pipe	Mixed	Cigarettes/day 1–9	10–19	20+	
"Exposed" gasworkers	8.3	10.2	6.7	4.4	18.1	38.5	13.9	3.61
Other gasworkers	5.8	15.3	5.9	6.2	17.8	35.5	13.4	1.49

[a] Per 100,000 per year standardized for age.

$$3000 \text{ ng/m}^3 \times 0.27 = 810 \text{ ng/m}^3 \text{ BP-AP}$$

where $0.27 = 5/7 \times 49/52 \times 0.4 \ldots$ 5/7 is the proportion of working days in a week, 49/52 is the proportion of working weeks in a year, and 0.4 is the proportion of air breathed at work in a working day; and writing the BP exposure as BP-AP (i.e., BP-air pollution) is to remind us that BP exposure has been expressed as average exposure and that BP is being considered as a marker of the carcinogenicity of the air.

To quantitate the excess lung cancer risk in a way that will make it applicable to general air pollution, a number of additional facets of the workers' exposure must be estimated. From our discussion of smoking-related lung cancer, we found that both the current age of the person and his age at starting to smoke were important in determining his risk of lung cancer. It is therefore obvious that both current age and age at starting work as a carbonization worker will be important in determining a carbonization worker's lung cancer risk. From the papers of Doll *et al.* (*7, 8*) one may estimate the average age of the workers at the midyear of the study to be about 58 years and their average length of time exposed as 23 years. However, this does not necessarily imply that their average age at starting such employment was 35 (i.e., 58−23) years, since "the men regularly change from one type of work to another" (*8*). We have, therefore, considered the two extreme possibilities: that they started such work at age 20 or that they started such work at age 35. In both situations we assume, however, a 23-year exposure by age 58 years.

1. Exposure Starts at Age 20

Over the 38 (58−20) years since starting to work the exposed worker would be exposed at work to an average of

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$$810 \text{ ng/m}^3 \times 23/38 = 490 \text{ ng/m}^3 \text{ BP-AP}$$

(where 23/38 is the proportion of working life exposed), again measured in air pollution equivalent terms. It is this exposure that "caused" the 142% increase in lung cancer risk. This increase is, however, in a lung cancer rate as determined by smoking habits averaging about 10 cigarettes a day. Such smoking habits in British unexposed workers would be responsible for some 87% of the lung cancer rate [this figure of 0.87 is obtained from Eq. (2) with $c = 20$ to allow for twice the effect of "British cigarette smoking" and $w = 20$]. We may express the three relevant lung cancer rates in terms of the rate in the unexposed workers, so that

"background" rate = 0.13
unexposed workers rate = 1.0
(smoking 10 cigarettes/day)

and

exposed workers rate = 2.42
(smoking 10 cigarettes/day)

An additive rather than a multiplicative (or synergistic) model for the combined effect on lung cancer risk of cigarette smoking and air pollution would appear more likely to reflect accurately the truth. Thus, since age at starting to smoke and age at starting exposure are nearly equal, we may write

$$10 \text{ British cigarettes} = 1.0 - 0.13 = 0.87$$

and

$$490 \text{ ng/m}^3 \text{ BP-AP} = 2.42 - 1.0 = 1.42$$

Using these two equations, it is a simple matter to express BP-AP in British cigarette terms; we find

$$30.0 \text{ ng/m}^3 \text{ BP-AP} = 1 \text{ British cigarette}$$

or

$$15.0 \text{ ng/m}^3 \text{ BP-AP} = 1 \text{ U.S. cigarette}$$

2. Exposure Starts at Age 35

The preceding equating of 15 ng/m^3 BP-AP with 1 U.S. cigarette was based on the assumption that the 23-year average exposure of the carbonization workers started at age 20. If instead we make the opposite extreme assumption that they started work at the latest possible time, i.e., at age 35, then during their life as carbonization workers they were exposed to 810 ng/m^3 BP-AP (see above). To

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express this exposure in cigarette equivalent terms we need to use Eqs. (2) and (4).

Equation (2) with $t = 58$, $w = 20$, and $c = 20$ (2×10 British cigarettes) gives us the lung cancer rate in unexposed workers, and Eq. (4) with $t = 58$, $w_1 = 20$, $c_1 = 20$, $w_2 = 35$, and some unknown c_2 will give us the rate in exposed workers. [Note that we are assuming here that exposure starting at age 35 is equivalent to smoking an additional $(c_2 - c_1)$ cigarettes per day from then on.] We saw that the results of Doll *et al.* (8) showed that the ratio of these rates (exposed/unexposed) was 2.42, and solving Eq. (4) to make this true gives us a value of c_2 of 53.2. Thus, we may write

$$810 \text{ ng/m}^3 \text{ BP-AP} = (53.2 - 20) = 33.2 \text{ U.S. cigarettes}$$

or

$$24.4 \text{ ng/m}^3 \text{ BP-AP} = 1 \text{ U.S. cigarette}$$

This is *up* from the 15.0 ng/m³ BP-AP when we assumed that the exposure began at age 20. If instead of using Eq. (4) we use Eq. (5), we find

$$810 \text{ ng/m}^3 \text{ BP-AP} = 74.0 \text{ U.S. cigarettes}$$

or

$$10.9 \text{ ng/m}^3 \text{ BP-AP} = 1 \text{ U.S. cigarette}$$

This is *down* from the 15.0 ng/m³ BP-AP when we assumed that the exposure began at age 20.

We do not know which of these assumptions about age at starting as a carbonization worker is closer to the truth, and taking the evidence as a whole we interpret this study as showing that approximately

$$15 \text{ ng/m}^3 \text{ BP-AP} = 1 \text{ U.S. cigarette}$$

We may now use this last equality and Eq. (2) to predict two quantities of epidemiologic interest, namely, the relative lung cancer rates in never-smokers exposed to different levels of air pollution and the "lifetime" risk of lung cancer from such exposure.

A never-smoker with lifelong exposure to air pollution at a level of b ng/m³ BP-AP will have a lung cancer incidence rate at age t of

$$I_{b/15}(t) = a(t-2)^{4.5} + 2.5a(b/15)(t-2)^{3.5}$$

[This is Eq. (2) with $w = 0$ and $c = b/15$.] The relative lung cancer incidence rates in never-smokers exposed to different levels of air pollution can be easily calculated from this and the results are shown in Table VII. These predictions can be compared to direct epidemiologic studies of these relative rates (see below).

The above formula [i.e., $I_{b/15}(t)$] may also be used to calculate for never-

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TABLE VII

Calculated Relative Lung Cancer Incidence in Never-Smokers Subject to Different Levels of BP-AP when 15 ng/m³ BP-AP is Equated to One U.S. Cigarette

BP-AP (ng/m³)	Relative incidence rate[a]
0	1.00
0.4[b]	1.07
1	1.17
2	1.33
5	1.83
6[c]	2.00
10	2.67

[a] Relative to a rate of 1.00 in never-smokers exposed to a zero level of BP-AP.

[b] Median value in "rural" areas in 1958–1959.

[c] Median value in "urban" areas in 1958–1959.

smokers exposed to different levels of air pollution both the cumulative incidence of lung cancer over a "standard lifespan" of 70 years and also that part of it arising from the air pollution—some illustrative results are given in Table VIII (these values may be compared to a calculated background cumulative rate of 435/100,000).

TABLE VIII

Calculated Cumulative Lung Cancer Incidence to Age 70 Due to Different Levels of BP-AP when 15 ng/m³ BP-AP is Equated to One U.S. Cigarette

BP-AP (ng/m³)	Cumulative incidence rate/100,000
0.014	1
0.1	7
1	73
5	363
10	724
20	1443

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B. United States Coke-Oven Workers

Lloyd and his colleagues (*29, 35*) found in their cohort studies of United States steelworkers that coke-oven workers experienced a substantial excess risk of lung cancer. When compared to "nonoven" workers at the same plants, the coke-oven workers as a group had 2.8 times the lung cancer mortality rate, and coke-oven workers who had more than five years "topside" exposure had 6.9 times the lung cancer mortality rate. No data were given on the smoking habits of these workers or those of unexposed workers, on length of employment, age, or average BP exposure. However, Jackson *et al.* (*26*) found average BP concentrations on the battery roof of a coke manufacturing plant of 6700 ng/m^3. If this is taken as the BP exposure of the topside workers then these results are remarkably compatible with those of the British carbonization workers discussed above.

The British carbonization workers had a relative risk of lung cancer of 2.42 at an exposure of 3,000 ng/m^3 BP, so we may write

unexposed British lung cancer rate = 1.0
carbonization workers rate = 2.42
increment per 1000 ng/m^3 BP exposure = 1.42/3 = 0.47

At the time of these surveys, the age adjusted United States national lung cancer mortality rate was just half of the British rate (*17,38*), so that taking this fact together with the relative risk of 6.9 for the United States topside workers, we may write

unexposed U.S. lung cancer rate = 0.5
topside workers rate = 0.5 × 6.9 = 3.45
increment per 1000 ng/m^3 BP exposure = (3.45 − 0.5)/6.7 = 0.44

This experience of coke-oven workers in the United States steel industry is thus in almost complete agreement with the British data, and the discussion of the British data in air pollution terms may be considered as applying to these data as well.

C. United States Hot Pitch Workers

In a cohort study of roofers working with hot pitch for more than 20 years, Hammond *et al.* (*19*) found a 1.59-fold increased lung cancer mortality rate compared to the general United States population. These workers were exposed to an average BP level of roughly 2000 ng/m^3. Similar calculations to those given above for United States coke-oven workers shows that these data suggest a risk per unit BP exposure about one-third that calculated from the British carbonization worker study. Some of this discrepancy may arise from using the

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general population as a comparison group. In the British carbonization worker study the unexposed workers had lung cancer rates some 25% lower than the national figures; if this "correction factor" is applied to this study of roofers then the roofers' data suggest a risk per unit BP exposure about 65% that calculated from the British carbonization worker study. When one considers the crudity of the exposure measurements and their "summary" by level of BP alone, this level of agreement must be considered remarkable.

D. "Urban/Rural" Differences in Lung Cancer Rates of Never-Smokers

Haenszel and his colleagues (*14*, *15*) obtained the smoking and residence histories for a 10% sample of all white female lung cancer deaths in the United States in 1958 and 1959, and for a 10% sample of all such deaths in white males in 1958. This data was compared to such information from a very large sample of the general population. These studies provide the clearest information on lung cancer risk by residential history in never-smokers: their results for "lifetime" residents of either urban or rural areas are given in Table IX.

The urban/rural ratio for males is probably inflated by a spuriously low rate in rural men (rural women have a 28% increased rate compared to such men) and by some lung cancer from industrial exposure. In 1958–1959 the median concentration of BP in urban air was approximately 6 ng/m^3 and in rural air was approximately 0.4 ng/m^3 (*37*). Table VII shows that equating 15 ng/m^3 BP-AP to 1 United States cigarette predicts an urban/rural ratio of 2.00/1.07 = 1.9, in almost complete agreement with the observed result of 1.7 for women.

This level of agreement is again remarkable, especially when one considers that we chose 15 ng/m^3 as a "representative" value for the possible values that could be calculated from the British gas-workers study, and also that the definitions of rural and urban are not completely comparable in Haenszel's

TABLE IX

Age-Adjusted Lung Cancer Death Rates per 100,000 of Never-Smokers by Sex for "Lifetime" Residents[a]

"Lifetime" residence	Death rate	RR[b]	Death rate	RR
Urban	12.5	3.2	8.4	1.7
Rural	3.9	1.0	5.0	1.0

[a] From Haenszel and Taeuber (*15*), Table 23.

[b] RR = Relative risk compared to "lifetime" rural residents.

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epidemiologic studies (*14, 15*) and in Sawicki's air pollution studies (*37*). It is very reassuring that calculations based on extreme industrial exposure give results very close to those one may have made using urban/rural differences in never-smokers, and it gives one a great deal of confidence in the results.

Other studies of urban/rural differences generally support the above conclusions [see Pike *et al. (34)* for references], although no gradient was noted in the large American Cancer Society study (*18*).

IV. CONCLUSIONS

Considering the evidence as a whole, it appears most reasonable to equate 15 ng/m^3 BP-AP with 1 United States cigarette (old style) in terms of lung cancer risk. From this conclusion one may then estimate the "single cause lifetime risk" (*30*) (cumulative risk to age 70) for different levels of BP-AP (Table VIII). We note that even at the low BP-AP level of 1 ng/m^3 the lifetime risk is slightly greater than 1/1500. Environmental regulations are usually made to keep such a risk to 1/10^5 or even 1/10^6.

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Lungenkrebs bei Angehörigen der Berufsgruppen „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung"

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Zusammenfassung

Unter 82 Lungenkrebspatienten der Berufsgruppen „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung" (= „Chemie") waren signifikant mehr Zigarettenraucher (96%) als unter den 169 Kontrollpersonen (77%). Signifikante Unterschiede zwischen Patienten und (Kontrollen) bestehen bei: *Jahre geraucht:* 41,6 (35,2); *Teerexpositionswert (TEW):* 2 437 (1 957). Raucher weisen gegenüber Niemalsrauchern mit R = 7,8 ein signifikant höheres Lungenkrebsrisiko (standardisiert nach Alter und TEW) auf. Raucher der Gruppe „Chemie" weisen nach Adjustierung von Alter, Berufsdauer und TEW gegenüber Rauchern der Gruppe „white collar" ein etwas erhöhtes Lungenkrebsrisiko (R = 1,3) auf. Signifikante Werte bestehen für eine Berufsdauer von weniger als 10 Jahren (R = 1,6) sowie 11–20 Jahren (R = 2,7).

Key-Words: Lung cancer – Occupation production and processing of rubber, dyes, and chemicals – Smoking habits – Lung cancer risk – Occupational exposure

Einleitung

Um die Bedeutung berufsbedingter Expositionen für das Lungenkrebsrisiko abzuschätzen, haben wir das Datenmaterial einer Fall-Kontroll-Studie, die 1 580 männliche Lungenkrebspatienten und 3 160 Kontrollpersonen (Erhebungszeitraum 1977–1979) umfaßt, nach Berufsgruppen analysiert. Wir haben an dieser Stelle über die Berufsgruppen „Metallgewinnung und -verarbeitung" (*Vutuc, Kunze,* 1981) und „Chauffeure" (*Vutuc, Kunze,* 1982) berichtet. Die vorliegende Arbeit analysiert die Rauchgewohnheiten von Angehörigen der Berufsgruppen „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung" sowie das berufsbedingte Lungenkrebsrisiko. Dieses konnte nur bei Zigarettenrauchern ermittelt werden, da wegen der kleinen Zahl von Niemalsrauchern unter den Patienten des Untersuchungs- und Vergleichskollektivs eine entsprechende Auswertung nicht durchgeführt werden konnte.

Patientengut und Methodik

Über die Durchführung und Methodik der Fall-Kontroll-Studie haben wir an anderer Stelle ausführlich berichtet (*Vutuc, Kunze,* 1981); sie gelten analog für diese Arbeit.

Aus dem Gesamtkollektiv (1 580 Patienten, 3 160 Kontrollpersonen) wurden alle Personen der Berufgruppen „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung" (= „Chemie") ermittelt und ihre Angaben über Alter, Rauchstatus und Dauer der Berufstätigkeit erhoben. Von den Zigarettenrauchern wurden Rauchdauer sowie alle jemals konsumierten Zigarettenmarken, einschließlich jeweiliger Menge und Konsumdauer, ermittelt. Die angegebenen Zigarettensorten wurden je nach Teergehalt einer von drei Markengruppen (*Kunze, Herberg, Vutuc,* 1978) zugeordnet (Gruppe I: <15 mg/Zig.; Gruppe II: 15–24 mg/Zig.; Gruppe III: >24 mg/Zig.). Der Teerexpositionswert (= TEW) wurde berechnet, indem die Summe der Produkte aus Zigarettenkonsum/Tag x Konsumdauer/Jahre x Gruppenfaktor (= 1, 2, 3) aller angegebenen Zigarettensorten gebildet wurde (*Vutuc,* 1980).

Als Vergleichskollektiv für die Berechnung des berufsbedingten Lungenkrebsrisikos der Zigarettenraucher der Berufsgruppe „Chemie" wurden aus dem Gesamtkollektiv alle Personen ermittelt, bei denen anamnestisch eine berufliche Exposition (Inhalationsnoxen) ausgeschlossen werden konnte (= „white collar"). Von den 784 Zigarettenrauchern (248 Patienten, 536 Kontrollpersonen) der 1 091 Personen, die der Gruppe „white collar" angehörten, wurde analog der TEW berechnet sowie Alter und Berufsdauer ausgewertet.

Das Lungenkrebsrisiko, adjustiert nach Alter und TEW, wurde für Zigarettenraucher der Berufsgruppe „Chemie" gegenüber Zigarettenrauchern der Gruppe „white collar" für unterschiedliche Dauer der Berufstätigkeit berechnet (*Mantel, Haenszel,* 1959). Das Alter wurde nach Kategorien unter 55, 56 bis 65, und über 66 Jahre adjustiert, der TEW nach den Kategorien <1 000, 1001–2000, 2 001–3 000, 3 001–4 000, >4 001. Die 95% Konfidenzintervalle wurden nach der Methode von *Miettinen* (1976) berechnet. Wegen der relativ kleinen Zahl von Bronchuskarzinompatienten wurde auf eine getrennte Analyse der Daten für Patienten mit einem Tumor der Gruppe Kreyberg I bzw. Kreyberg II verzichtet.

Ergebnisse

Von den 1 580 Patienten und 3 160 Kontrollpersonen des Gesamtkollektivs wurden 82 Patienten und 169 Kontrollpersonen der Berufsgruppe „Chemie" zugeordnet. 72 (88%) der 82 Patienten hatten einen Tumor der Gruppe Kreyberg I, 10 Patienten einen Tumor der Gruppe Kreyberg II.

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Von den 82 Patienten waren 79 (96%) Raucher, von den 169 Kontrollpersonen haben 131 (77%) geraucht (jeweils einschließlich Exraucher). Patienten haben signifikant häufiger (χ^2 12,97; $p < 1\%$) geraucht als Kontrollpersonen. Es wurden ausschließlich Zigaretten konsumiert.

Die Niemalsraucher unter den Patienten (3 Personen) waren zum Zeitpunkt der Diagnose durchschnittlich 62,8 Jahre alt (SF = 7,06) und waren durchschnittlich 24,3 Jahre (SF = 8,71) berufstätig. Die 38 Kontrollpersonen, die niemals geraucht haben, waren zum Befragungszeitpunkt durchschnittlich 64,3 Jahre alt (SF = 1,59) sowie 33,3 Jahre (SF = 1,61) berufstätig.

In Tab. 1 sind die Durchschnittswerte für Alter, Dauer der Berufstätigkeit, Jahre geraucht und Teerexpositionswert der Raucher unter den Patienten und Kontrollpersonen dargestellt.

Tab. 1 Männliche Bronchuskarzinompatienten und Kontrollpersonen, Berufsgruppen „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung", Durchschnittswerte für Alter, Berufsdauer, Rauchdauer und Teerexpositionswert (1 SF).

	Patienten (n = 79)	Kontrollen (n = 131)
Alter zum Diagnosezeitpunkt	65,9 (1,01)	63,7 (0,80)
Jahre berufstätig	27,6 (1,48)	29,7 (0,99)
Jahre geraucht	41,6* (1,15)	35,2 (1,21)
Teerexpositionswert	2437** (219)	1957 (104)

* $p < 1\%$; ** $p < 5\%$

Patienten haben signifikant länger ($t = 3.56$; $p < 1\%$) geraucht und weisen einen signifikant höheren ($t = 2,21$; $p < 5\%$) TEW auf als Kontrollpersonen.

Raucher (einschließlich Exraucher) der Berufsgruppe „Chemie" weisen mit einem Risiko von 7,8 (95% Vertrauensbereich: 4,4–13,8) gegenüber Niemalsrauchern (R = 1,0) ein signifkant höheres (χ^2 48,249; $p < 1\%$) Lungenkrebsrisiko (adjustiert für Alter und TEW) auf.

Für die Bestimmung des berufsbedingten Lungenkrebsrisikos von Rauchern des Samples „Chemie" wurde ein Sample von 784 Rauchern (248 Patienten, 536 Kontrollpersonen) der Gruppe „white collar" als Vergleichskollektiv verwendet. In Tab. 2 ist das Lungenkrebsrisiko (adjustiert nach Alter und TEW) von Rauchern der Gruppe „Chemie" gegenüber Rauchern der Gruppe „white collar" nach Dauer der Berufstätigkeit dargestellt. Signifikante Unterschiede bestehen bei einer Berufsdauer von weniger als 10 Jahren (χ^2 5,680; $p < 5\%$) sowie 11 bis 20 Jahren (χ^2 4,590; $p < 5\%$).

Diskussion

Mit der Ausnahme von 3 Personen waren alle Lungenkrebspatienten der Berufsgruppe „Chemie" Zigarettenraucher (96%). Gegenüber den Rauchern in der Kontrollgruppe weisen sie ein extremes Konsumverhalten auf (signifikante Unterschiede bei Rauchdauer und TEW). Entsprechend stellen die Tumoren der Gruppe Kreyberg I mit 88% den dominierenden Anteil der histologischen Typen. Zigarettenraucher weisen gegenüber Personen, die niemals geraucht haben, ein etwa 8fach höheres Lungenkrebsrisiko auf. Diese Ergebnisse stimmen weitgehend mit den Ergebnissen einer Untersuchung (*Kunze, Vutuc,* 1980; *Vutuc,* 1980) überein, die an einem gepoolten Sample, ohne Berücksichtigung der Berufszugehörigkeit, durchgeführt worden war. Es kann daraus geschlossen werden, daß im vorliegenden Kollektiv der Berufsgruppe „Chemie" das Zigarettenrauchen die dominierende ätiologische Noxe für das Entstehen des Bronchuskarzinoms darstellt.

Raucher der Berufsgruppe „Chemie" weisen gegenüber den Rauchern des Vergleichskollektivs, nach Kontrolle von Alter und Rauchgewohnheit (TEW) als mögliche Vermengungsfaktoren, ein geringgradig (R = 1,3) erhöhtes Lungenkrebsrisiko auf. Eine Dosis-Wirkungs-Beziehung (Anstieg des Risikos mit Zunahme der Berufsdauer) konnte nicht nachgewiesen werden; eher eine Abnahme des Risikos mit zunehmender Berufsdauer (signifikante Werte: R = 1,6 für Berufsdauer weniger als 10 Jahre sowie R = 2,7 für Berufsdauer 11–20 Jahre). Ein tatsächlich bestehendes Überschußrisiko ist daher in erster Linie für jene Raucher der Berufsgruppe „Che-

Tab. 2 Lungenkrebsrisiko (adjustiert nach Alter und Teerexpositionswert) von Zigarettenrauchern der Berufsgruppe „Gummi-Farbstoff-Chemikalienerzeugung und -verarbeitung" (CH) gegenüber Zigarettenrauchern der Gruppe „white collar" (WC) nach Dauer der Berufstätigkeit

	Jahre berufstätig										insgesamt	
	–10		11–20		21–30		31–40		40 +			
	CH	WC	CH	WC	CH	WC	CH	WC	CH	WC	CH	WC
Patienten	10	10	21	24	14	76	23	96	11	42	79	248
Kontrollen	11	26	20	68	43	159	39	214	18	69	131	536
RR	1,6		2,7		1,1		1,4		1,0		1,3	
95% Vertrauensbereich	1,2–2,3		1,2–6,2		0,5–2,3		0,8–2,5		0,4–2,4		1,0–1,7	
χ^2	5,68*		4,59*		0,1		0,9		0,1		3,26	

* $p < 0,5\%$

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mie" anzunehmen, die nicht länger als 20 Jahre in diesem Bereich tätig waren.

Die vorliegende Untersuchung hatte zum Ziel, festzustellen, ob in einem Berufsbereich, in dem mit Expositionen gerechnet werden kann, gegenüber Berufen, in denen Expositionen anamnestisch ausgeschlossen werden können, ein Überschußrisiko besteht. Qualitative und quantitative Aussagen über berufliche Noxen können aus dieser Analyse nicht abgeleitet werden. Dazu sind weitere Untersuchungen notwendig, die unter anderem auch Analysen technologischer Prozesse in den angeführten Berufssparten beinhalten. Diese würden auch die zeitliche Einordnung beruflicher Expositionen ermöglichen, d. h., ob die Exposition zu bestehenden oder nicht mehr in Verwendung befindlichen technologischen Prozessen in Beziehung zu setzen ist. Nur mit Hilfe der Ergebnisse dieser weiteren Untersuchungen können Interventionskonzepte ausgearbeitet werden, die die Eliminierung der beruflichen Risikofaktoren zum Ziel haben.

Neben der Fahndung nach kanzerogenen Gefahren am Arbeitsplatz darf jedoch nicht vergessen werden, daß der Tabakkonsum die wichtigste Noxe für das Entstehen von Lungenkrebs darstellt und im Gegensatz zu den beruflichen Noxen qualitativ und quantitativ einfach zu erfassen ist. Weiters erfordern Maßnahmen der gesundheitlichen Aufklärung bzw. Einrichtungen zur Raucherentwöhnung einen vergleichsweise geringen Aufwand. Aus präventivmedizinischer Sicht sollte daher, neben der Aufklärung kausaler Zusammenhänge mit berufsbedingten Noxen, versucht werden, eine Tabakabstinenz bei den Rauchern zu erzielen. Ein geringgradig erhöhtes Risiko, wie es für Raucher der Berufsgruppe „Chemie" nachgewiesen wurde, kann möglicherweise bereits durch eine Tabakabstinenz beeinflußt werden; denn die geringe Risikozunahme sowie die übereinstimmenden Ergebnisse (bezüglich: %-Kreyberg-I-Tumoren, %-Raucher, Rauchdauer, TEW) mit dem gepoolten Sample (*Kunze, Vutuc,* 1980; *Vutuc,* 1980), erlauben die Annahme, daß berufliche Faktoren hier eher die Wirkung der Noxe Tabak verstärken, als selbst kausal zu wirken.

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BUCHBESPRECHUNGEN

Boschke, W.L.: **Sozialökonomische Aspekte der Hypotonie.** (Schriftenreihe d. Instituts für Gesundheits-System-Forschung) 1981. 103 S. (Institut für Gesundheits-System-Forschung, Kiel.) Kart.

Herr *Boschke* legt eine sozialökonomische Studie über die Problematik der Hypotonie vor. Sie ist für jeden in der Praxis tätigen Arzt von größtem Interesse, da Herr *Boschke* sich mit der Häufigkeit und vor allem mit den Kosten befaßt, die die Allgemeinheit für Kreislaufregulationsstörungen aufbringen muß. Wer weiß schon, daß unsere Volkswirtschaft in der Bundesrepublik jährlich mit über 2 Milliarden DM durch die Diagnose Hypotonie belastet wird.

Der Interessierte findet eine Fülle von Daten über Häufigkeit der Hypotonie, Altersverteilung, Berufs- und Erwerbsunfähigkeit sowie Rentenanträge. Geschickt dargestellte Graphiken vereinfachen eine rasche Information.

H. Rieckert, Kiel

Rechtsanwalt *Donatus v. Renthe-Fink:* **Meine sozialen Rechte.** 183 S. (Walhalla u. Praetoria Verlag KG, Regensburg.) Kunstledereinband, DM 12,80.

Die Kompliziertheit der rechtlichen Grundlagen unserer sozialen Sicherung macht es dem betroffenen Bürger immer schwieriger, diese gesetzlichen Grundlagen und damit auch seine Rechte und Pflichten zu kennen. Das Buch von v. *Renthe-Fink* „Meine sozialen Rechte" informiert über die Rechtsgrundlagen aller Zweige der sozialen Sicherung sowie über die Beratungsmöglichkeiten durch Behörden, Versicherungen und Dritte. Jeder Bürger kann sich anhand dieses Büchleins konkret und umfassend über die Ansprüche unterrichten, die er an den Staat und an Versicherungen hat. Dabei wird es erneut wegen der Kompliziertheit der Materie unverändert notwendig sein, die Beratung von Sachkundigen in Anspruch zu nehmen. Aber gerade auch hierfür weist dieses Buch die notwendigen Wege.

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LUNG CANCER

Etiology, Epidemiology, Prevention, Early diagnosis, Treatment

Proceedings of the 1st European Symposium on Lung Cancer
Chalkidiki, September 7–13, 1980

Editor:
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Quantification of cigarette tar exposure and lung cancer risk: Aspects of prevention and early detection

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Lung cancer epidemiology has undoubtedly led to some of the most important results in cancer research. Among many other findings the clear dose-response relationship between tobacco consumption and lung cancer risk offers interesting areas not only for further research but also for intervention techniques. Acknowledging the fact that lung cancer treatment has already established its possibilities and no dramatic progress is to be expected, we have to focus our interest on prevention and early detection of this man made cancer.

The modern lung cancer epidemiology provides not only ideas on how to improve lung cancer control but also first answers to important questions in this field. Some examples are as follows: (a) Prevention of lung cancer is possible in the order of 85% of all cases, complete abstinence from tobacco consumption in a given population being the theoretical background. (b) Ever increasing evidence shows that lung cancer risk could also be lowered by either changing individual smoking habits and/or by modification of the tobacco product, especially the cigarette. While these possibilities cannot be compared with the benefits of non-smoking, they have to be taken into consideration too because millions of people still smoke and millions of youngsters will start in the future. (c) The epidemiology of lung cancer in the decades to come will definitely show whether the concept of reducing the cancer risk among smokers is working in terms of noticeable changes in morbidity. (d) Screening for lung cancer – if it is to be of any benefit – has to be designed according to the epidemiological findings. High-risk groups are to be screened, such groups being defined according to the smoking histories of the individuals involved.

Our contribution will hopefully be of some help in both areas: prevention and early detection; it is an analysis of lung cancer risk in relation to the life long tar exposure in cigarette smokers. Our considerations are also based on the numerous retrospective and prospective epidemiological studies already available including our own work. In a nationwide retrospective study, lung cancer patients and appropriate controls were interviewed about all relevant life style factors (6, 7). This work led us to the development of a formula for quantifying tar exposure (10) which will be demonstrated further on.

In the course of the epidemiological investigations on lung cancer in

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Austria, we detected two important circumstances: (a) The average smoking history of the smokers and smoking lung cancer patients is not homogenous as far as daily consumption and favourite brands are concerned. The considerable changes in smoking habits among the relevant age groups should be observed and taken into account. Due to economic reasons and other factors, e.g. availability of cigarettes during and after the WWII, daily consumptions are not relatively stable variables for epidemiologists. (b) The cigarette market underwent important changes during the last decades; especially, the tar content of cigarettes decreased considerably. This has to be considered as well, along with the switching of brands with different tar contents during the life-long smoking career of a tobacco consumer.

These considerations are derived mainly from the local Austrian situation which is undoubtedly different from the tobacco market and the smoking habits in e.g. the U.S.A. where many studies have been conducted in the past.

CALCULATION OF TAR EXPOSURE

The current and previous cigarette brands were grouped into three categories according to their tar yields (Group I: below 15 mg, Group II: 15-24 mg, Group III: more than 25 mg). The tar yields used are those determined and published by the Austrian Tobacco Monopoly (1). The problem of the relatively high tar yield figures obtained by the measurement procedure used in Austria is solved by implementing factors for each group (Group I = 1, Group II = 2, Group III = 3). The formula itself uses information about all brands ever smoked, their specific tar yield, the duration of, and all variations in daily consumption (10).

$$TE = \sum_{ij=1}^{n} (a_{x_i} b_{x_j}) k_x + \sum_{ij=1}^{n} (a_{y_i} b_{y_i}) k_y + \sum_{ij=1}^{n} (a_{z_i} b_{z_i}) k_z$$

where a_x, a_y, a_z = cigarette consumption per day in Groups I-III; b_x, b_y, b_z = years of cigarette consumption in Groups I-III; and k_x, k_y, k_z = group factor.

Thus, for example, a smoker who smoked 30 high-tar cigarettes/day (Group III) for 20 years, 2 packs/day of another brand of Group III for 14 years, 2 packs/day of a medium-tar cigarette (Group II) for 9 years, and 1 pack/day of a low-tar cigarette (Group I) for 1 year has a tar exposure of 4220. The calculation is: 30 (cigarettes) x 3 (group factor) x 20 (years) = 1800 + 1680 (40 x 3 x 14) + 720 (40 x 2 x 9) + 20 (20 x 1 x 1).

This formula is a first step and, of course, only additional information and is not meant to replace the usual analysis by the known variables. It is also incomplete and could be supplemented by information about inhalation, butt length and other characteristics of tobacco apart from tar yields.

In contrast to many remaining problems with this formula, some unsolveable questions and the possible and given disadvantages of any simplification

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of a very complex situation, some favorable aspects of a simple quantification of tar exposure should be mentioned: (a) rather complex and changing smoking habits may be described more easily than by other means; (b) the changing market structure and the changing tar contents of cigarettes can be implemented into statistical analysis; (c) high-risk groups may be identified more easily and accurately, and thus the resources can be better aimed at those groups which are extremely exposed smokers; (d) for health education purposes a simple formula might be quite impressive for tobacco consumers and would add motivational elements to the precessation process; (e) last but not least, the formula might be helpful in trying to define a threshold for lung cancer risk in smokers. The discussion about this topic is now in progress and remains one of the most important scientific problems in the area of applied cancer research.

TAR EXPOSURE: RESULTS AND EXAMPLES OF APPLICATION

The following should demonstrate how quantitative information about the tar exposure to smokers could be used to: compare lung cancer patients and controls; show differences between male and female patients and controls; calculate relative risks of smokers compared to non-smokers; contribute to the question of possible thresholds of lung cancer risk; check how actual smoking habits are related to these thresholds; identify high-risk groups for screening.

Lung cancer patients and controls

The average tar exposure in male tumor patients is significantly higher than the tar exposure in controls. Using the smoking histories of 414 patients and 828 controls in all age groups (395 or 95% of the cases being smokers or ex-smokers compared to 620 or 75% of the controls) the following average tar exposures were calculated: 2596 for smoking cancer patients, 2026 for smoking controls (significant at $P < 1\%$). There is also a significant difference between Kreyberg I tumors (TE 2616), squamous cell carcinoma cases (TE 2628) and controls, but not between Kreyberg II tumors (TE 2421) and controls.

In the age groups 51-60 and 41-50 respectively, we found the same distribution pattern of tar exposure, although the absolute figures are somewhat different due to the relatively shorter smoking careers especially in the youngest age group.

Female patients and controls

The average tar exposure in a female tumor patient is significantly higher than the average tar exposure in female controls; but it is significantly lower than the average tar exposure in a male patient.

Using the smoking histories of 200 patients and 400 controls (117 or 59%

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of the cases being smokers or ex-smokers compared to 86 or 22% of the controls) the following average tar exposures were calculated: 1824 for smoking cancer patients, 1200 for smoking controls (significant at $P < 1\%$). There is also a significant difference between Kreyberg I tumors (TE 1874), squamous cell carcinoma cases (TE 1662) and controls, but not between Kreyberg II tumors (TE 1579) and controls.

In Austria lung cancer in females is less frequent than in males because the percentage of tobacco consumers is lower in females than in males, and moreover, the average tar exposure in the female smoker is lower than that in the male smoker. Both factors contribute to the fact that less females compared to males are at high-risk for lung cancer.

The years to come will show a continuous rise in lung cancer morbidity among females since the smoking habit is still spreading (in contrast to males) and the average daily consumption is increasing (11).

Relative lung cancer risk for smokers

Tar exposure is of course related to lung cancer risk in a dose-response relationship – Table 1 gives the figures for males and females (9, 10, 12). Most interesting is the fact that tar exposure and risk for Kreyberg II tumors are also linked in females.

Question of thresholds

It has already been stated clearly that non-smoking is the optimal strategy to prevent lung cancer. Discussing thresholds of lung cancer risk should never lead to the conclusion that continuation of smoking is a good advise to tobacco consumers under certain circumstances. But reality presents the picture of the smoking epidemic and therefore we have to discuss what we can achieve for those who cannot or do not want to stop smoking.

We strongly believe in a comprehensive and complex system of intervention to control lung cancer which, among other strategies, also includes product modification of cigarettes (3, 8). Lowering tar yields is one of the most important goals in this respect.

Checking our results in order to contribute to the question of thresholds of lung cancer risk, one identifies tar exposures in the range of 500-1000 which might be of help in discussing the point further. This tar exposure range has to be compared with the actual situation of smoking habits in order to find out whether it is a realistic and feasible goal.

If the average Austrian smoker smokes the leading brand for 30 years with a daily consumption of 30 cigarettes he gains a tar exposure of 1800. This is still quite a high exposure. A young smoker who starts with a low tar cigarette and smokes only one pack per day and stops after 20 years gets a tar exposure of 400 which is in the range of a possible threshold for lung cancer risk. This assumption of a smoker's career is quite realistic because low tar brands are relatively popular among young smokers. But there are still the hard-core smokers, especially among the less educated males, who

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Table 1 Lung cancer risk and tar exposure (9, 10, 12)

Tumor types	Tar exposures						
	< 500	501-1000	1001-2000	2001-3000	3001-4000	4001-5000	> 5001
Males: All age groups							
All cancer types	1.6	2.4+	4.2+	5.8+	6.1+	7.4+	6.1+
Kreyberg I	2.0	2.6+	5.3+	7.2+	7.7+	9.5+	7.8+
Kreyberg II	–	1.8	1.8	3.5++	>3001:3.9		
Age 41-50 yr							
Kreyberg I	0.6	2.4	6.3+	9.1+	4.6++	4.6++	6.1++
Kreyberg II			> 1001: 2.1				
Age 51-60 yr							
All cancer types	0.8	2.1	6.5+	9.0+	8.7+	6.6+	8.4+
Kreyberg I	1.0	4.1++	15.7+	21.5+	20.8+	17.1+	21.5+
Kreyberg II	0.6	1.0	1.2	3.3	3.0	–	–
Females: All age groups					>3001		
All cancer types	1.1	2.1+	3.5+	3.3+	3.2+		
Kreyberg I	1.5	4.2+	4.8+	4.9+	6.8+		
Kreyberg II	–	1.1	3.1+	–	2.3++		

+P < 1%; ++P < 5%.

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prefer non-filter, high tar cigarettes and who have been smoking at least a pack per day for an average of 35 years. Such smoking history gives a tar exposure of over 2000 and makes the individuals concerned candidates for lung cancer.

Identification of high-risk groups for screening

Early detection of lung cancer is related to the chance of cure, and the organization of screening programs is now a topic of intensive scientific and public discussion. Recently, the American Cancer Society released rather pessimistic statements about the value of screening for lung cancer.

Based on the epidemiological situation in Austria and first experiences of the Mayo-Lung-Project (2), we calculated that in a high-risk group of smokers (more than 20 cigarettes a day for more than 20 years) 1.4% lung cancer cases could be detected by an intensive screening program including X-ray and cytology. Undoubtedly, the application of our formula for tar exposure could lead us to a more precise definition of people at extreme risk. These should be screened first, also because of the excess morbidity caused by other tobacco related diseases.

It is not lung cancer alone which supports the need for special health check-ups for heavy smokers. Therefore, we developed PROGRAM 20 x 20 (20 cigarettes daily for 20 years) which focuses on several tobacco related diseases including lung cancer and also offers a smoking withdrawal treatment to the client (4, 5).

SUMMARY

A formula to quantify the tar exposure in smokers is described; it is based on information about the life-long smoking habits of the individual and offers some aspects to the prevention and early detection of lung cancer: rather complex and changing smoking habits may be described more easily than by other means; the changing market structure and the changing tar content of cigarettes can be implemented into statistical analysis; high-risk groups may be identified more easily and accurately, and thus the resources can be better aimed at those groups which are extremely exposed smokers; for health education purposes a simple formula might be quite impressive for tobacco consumers and would add motivational elements to the precessation process; last but not least, the formula might be helpful in trying to define a threshold for lung cancer risk in smokers. The average tar exposure in male tumor patients is significantly higher than that in controls. There is a significant difference between Kreyberg I tumors, squamous cell carcinoma cases and controls but not between Kreyberg II tumors and controls.

The average tar exposure of a female tumor patient is significantly higher than the average tar exposure of female controls; but it is significantly lower than the average tar exposure of a male patient. Tar exposure is of course related to lung cancer risk in a dose-response relationship.

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To contribute to the question of thresholds of lung cancer risk, one identifies tar exposure which might be of help in discussing this matter further.

The application of the formula for tar exposure could lead to a more precise definition of people at extreme risk. These should be screened first, also because of the excess morbidity caused by other tobacco related diseases.

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EVENTIVE MEDICINE 11, 713–716 (1982)

SHORT REPORT

Lung Cancer Risk in Women in Relation to Tar Yields of Cigarettes[1]

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Of 297 female lung cancer patients studied, 188 or 63% were cigarette smokers, significantly ($P < 1\%$) more than in the control group (119 = 21% of 580). In relation to women who had never smoked, the adjusted (for age, total years smoked, and average number of cigarettes smoked per day) lung cancer risk for smokers who had exclusively smoked cigarettes belonging to group I (<15 mg tar/cig.) was $R = 1.5$, for group II-type cigarettes (15–24 mg tar/cig.) $R = 2.7$ ($P < 1\%$), and for group III (>24 mg tar/cig.) $R = 6.3$. The risks for smokers who had smoked primarily cigarettes belonging to groups I, II, and III were $R = 2.6$, $R = 4.4$ ($P < 1\%$), and $R = 8.9$ ($P < 1\%$), respectively.

INTRODUCTION

The market shares of filter cigarettes increased from 8.8% in 1960 to 92.5% in 1977. Corresponding to this trend, the smokes values (measurement following ISO [illegible]) of the average Austrian cigarette decreased for tar by 54.5% from 33.67 mg/cig. to 15.3 mg/cig., and for nicotine by 63% from 1.95 mg/cig. to 0.72 mg/cig. (5). There is also evidence from U.S. studies that the tumorigenic potential of cigarette tar has decreased (12, 13); this might also apply for Austrian cigarettes, which are blended products similar to U.S. brands (5). From the viewpoint of preventive medicine, it is of major interest to determine how reductions of tar yield influence the lung cancer risk to the smoker. This article deals with the lung cancer risk of female smokers in relation to the tar yields of cigarettes smoked.

MATERIALS AND METHODS

In a case-control study described in detail elsewhere (7, 8, 11), 297 female patients with histopathologically confirmed lung cancer were interviewed at time of diagnosis using a standardized questionnaire (1, 8). The study was undertaken on a nationwide basis in 15 lung cancer centers in Austria from the end of 1976 through 1980. The control group consisted of 580 women, 50% drawn from inpatients at the hospital where the lung cancer patient was diagnosed, and 50% from the neighborhoods where the lung cancer patients lived. Controls were selected based on the absence of a tobacco-related disease and according to the age of the patient (±5 years). Tobacco-related disease was defined as a cancer of the lung, larynx, mouth, esophagus, bladder, pancreas, liver, or kidney; myocardial infarc-

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tion: stroke; peripheral vascular disease, abdominal disease, or abdominal aortic aneurysm; chronic bronchitis or chronic obstructive pulmonary disease; or gastric ulcer. In addition, patients with cirrhosis of the liver were excluded from the control group.

Of the 297 patients and 580 controls, 32 cases and 69 controls belonged to the age group up to 50 years, 58 cases and 128 controls belonged to the age group 51–60 years, 103 cases and 227 controls belonged to the age group 61–70 years, and 104 cases and 156 controls belonged to the age group above 70 years. The smoking histories of cases and controls (smokers and ex-smokers who only smoked cigarettes) included: all cigarette brands ever smoked and for each brand the duration of consumption and the number of cigarettes smoked daily. The cigarette brands reported by the respondents were allocated to one of three groups (6) according to their tar yields (2) (group I: < 15 mg of tar/cig.; group II: 15–24 mg/cig.; group III: >24 mg/cig.). Adjusted (age, duration, quantity) relative risks (9) were estimated in relation to women who had never smoked, smokers who only had smoked cigarettes belonging to group I, or group II, or group III, respectively, and smokers who had smoked cigarettes belonging to group I, or group II, or group III as the most dominating brands (at least 2/3 of the total duration of the smoking habit). Age categories used in the adjustment were: up to 50, 51–60, 61–70, and above 70 years. The respective categories for total duration of smoking habit: below 10, 10–19, 20–29, 30–39, 40 and more years and for average number of cigarettes smoked per day: up to 10, 11–20, more than 20 cig./day. The 95% confidence limits were calculated by the method of Miettinen (10).

RESULTS

One hundred and eighty-eight or 63% of the 297 female lung cancer patients were cigarette smokers (ex-smokers included); in the control group 21% (119 out of 580) were smokers. Patients significantly more often smoked cigarettes than controls (χ^2 156.14; $P < 1\%$). Table 1 shows the lung cancer risk adjusted for age, total duration of smoking habit, and average number of cigarettes smoked per day for women who had smoked exclusively or as dominating brands cigarettes belonging to group I, or group II, or group III in relation to women who had never smoked. A dose–response relationship can be demonstrated. There is a significant increase of lung cancer risk with the increase of tar yields of cigarettes consumed exclusively or as dominating brands.

DISCUSSION

Our results confirm previous studies (3, 4, 14) demonstrating a dose–response relationship between lung cancer risk and tar yields in female cigarette smokers. The interpretation of the results referring to group I cigarettes should be made carefully because of small sample sizes. It should also be noted that group I cigarettes became available in Austria only in the mid 1960's (5). Further epidemiological studies should therefore concentrate on cancer risk in smokers of low tar cigarettes.

These results may be translated into possible health policy goals as follows: It seems feasible to influence lung cancer risk by reducing tar yields and aiming for

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TABLE I

FEMALE CIGARETTE SMOKERS, LUNG CANCER RISK ADJUSTED FOR AGE, YEARS OF SMOKING HABIT, AND AVERAGE NUMBER OF CIGARETTES SMOKED PER DAY

	Exclusively cigarettes smoked belonging to:							
	Never smoked		Group I (<15 mg tar/cig.)		Group II (15–24 mg tar/cig)		Group III (>24 mg tar/cig.)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	109	461	1	3	19	29	23	15
I^r	1.0		1.5		2.7		6.3	
95% confidence interval			0.1–14.2		1.5–4.7		3.5–11.3	
χ^2			0.08		10.30*		35.07*	

	Cigarettes as dominating brands smoked belonging to:							
	Never smoked		Group I		Group II		Group III	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	109	461	4	6	50	49	134	64
R	1.0		2.6		4.4		8.9	
95% confidence interval			0.8–8.3		2.9–6.5		6.7–11.7	
χ^2			1.38		50.15*		227.16*	

* $P < 1\%$.

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greater market shares for low tar cigarettes. One should, however, see this development under the concept of a shrinking cigarette market. Although not smoking is the only really safe way to avoid lung cancer, reality tells us that people will continue to smoke for decades. Therefore, a first step would be removing high tar cigarettes (groups II and III of our classification) from the market. As already mentioned, further epidemiological studies on smokers of low tar cigarettes will be needed to define the upper limits of tar yields of cigarettes belonging to group I.

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Bronchuskarzinom und Zigarettenkonsum bei Frauen (Ergebnisse einer Fall-Kontroll-Studie)

Lung Cancer and Cigarette Smoking in Women (Results of a Case Control Study)

CHRISTIAN VUTUC

Abstract

Smoking habits of 297 female lung cancer patients (Kreyberg I: 202, Kreyberg II: 95) and 580 controls were analysed. In addition tar exposures (TE) were calculated. Calculation of TE includes amount of consumption, duration and the tar yields of all cigarette brands ever smoked. There are significant more smokers among patients (63%) and patients with a K I tumor (80%) compared to the controls (21%); K II: 29%. All patients and patients with a K I tumor had a significant longer smoking career (39.3 years; 39.6 years) and a higher tar exposure (TE = 1767; TE = 1810) compared to the controls (31.9 years, TE = 1146). K II: 37.4 years, TE = 1578. Lung cancer risks (adj. for TE) and population attributable risks (PAR) were: all age groups R = 7.3*, PAR = 54%; *< 40 years* R = 1.1, PAR = 3%; *41–50 years* R = 4.2*, PAR = 42%; 51–60 years R = 7.6*, PAR = 62%; 61–70 years R = 7.8*, PAR = 54%; > 71 years R = 8.0*, PAR = 55%. Lung cancer risks (adj. for age) in relation to tar exposure and attributable risks (AR) were: TE < 500: all cases R = 1.5, AR = 34% (K I R = 2.9, K II R = 0.8); TE 501–1000: all cases R = 4.2*, AR = 76% (K I R = 9.9*, K II R = 1.1); TE 1001–2000: all cases R = 12.1*, AR = 92% (K I R = 27.2*, K II R = 2.6**); TE 2001–3000: all cases R = 11.1*, AR = 91% (K I R = 25.2*, K II R = 2.0); TE > 3001: all cases R = 13.0*, AR = 92% (K I R = 29.3*, K II R = 3.3). There is a significant increase of risk of cigarette smokers beyond a TE of 501, which could be identified as a sort of critical exposure. There is a pronounced dose response relationship between cigarette smoking in relation to TE and lung cancer risk as concerning K I tumors but not K II tumors. Lung cancer risks in relation to age began smoking: *< 19 years* R = 7.8*; *19 years and above* R = 6.5*.

* $P < 1\%$, ** $P < 5\%$.

Zusammenfassung

Es wurden die Rauchgewohnheiten von 297 weiblichen Bronchuskarzinom-Patientinnen (Kreyberg I: 202, Kreyberg II: 95) und 580 Kontrollpersonen analysiert und das Lungenkrebsrisiko berechnet (Niemals-Raucherinnen R = 1,0). Signifikant mehr Patientinnen (63%) und Patientinnen mit einem K I Tumor (80%) waren Zigarettenraucher, haben signi-

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fikant länger geraucht (39,3 Jahre; 39,6 Jahre) und weisen einen signifikant höheren durchschnittlichen Teer-Expositionswert (TEW = 1767; TEW = 1810) auf als Kontrollpersonen (21%, 31,9 Jahre, TEW = 1146). K II: 28%, 37,4 Jahre, TEW = 1508. Das Lungenkrebsrisiko (adj. nach TEW) und das „population attributable risk" (PAR) betragen: Alle Altersgruppen R = 7,3*, PAR = 54%; < 40 Jahre R = 1,1, PAR = 3%; 41–50 Jahre R = 4,2*, PAR = 42%; 51–60 Jahre R = 7,6*, PAR = 62%; 61–70 Jahre R = 7,8*, PAR = 54%; > 71 Jahre R = 8,0*, PAR = 55%. Das Risiko (adj. nach Alter) in Relation zur Höhe des TEW sowie das beitragende Risiko (AR) betragen: TEW < 500: Alle Karzinome R = 1,5, AR = 34% (K I R = 2,9, K II R = 0,8); TEW 501–1000: Alle Karzinome R = 4,2, AR = 76% (K I R = 9,9*, K II R = 1,1); TEW 1001–2000: Alle Karzinome R = 12,1*, AR = 92% (K I R = 27,2*, K II R = 2,6**); TEW 2001–3000: Alle Karzinome R = 11,1*, AR = 91% (K I R = 25,2*, K II R = 2,0); TEW > 3001: Alle Karzinome R = 13,0*, AR = 92% (K I R = 29,3*, K II R = 3,3). Frauen, die vor dem 10. Lebensjahr mit dem Rauchen begonnen haben, weisen ein Lungenkrebsrisiko von R = 7,8* auf; nach dem 19. Lebensjahr R = 6,5*.

* P < 1%, ** P < 5%.

Einleitung

Die zunehmende Verbreitung des Tabakkonsums bei Frauen (18) findet in der Zunahme der Bronchuskarzinom-Sterblichkeit ihren Niederschlag. Von 1964 bis 1979 ist die Zahl der Todesfälle absolut um 45% (von 414 auf 599 Todesfälle) sowie relativ um 40% (von 10,8/100000 auf 15,1/100000) angestiegen. Trotz dieser zunehmenden Häufigkeit sind die Fallzahlen, verglichen mit den Männern, noch gering. Entsprechend finden sich in der Literatur wenig epidemiologische Untersuchungen, die sich mit der Frage Bronchuskarzinom und Tabakkonsum bei der Frau auseinandersetzen bzw. es handelt sich um Untersuchungen mit relativ kleinen Fallzahlen (Übersicht in 19).

Wir haben bereits zu dieser Fragestellung über erste Ergebnisse (15, 16, 17, 19) einer Fall-Kontroll-Studie berichtet. Nach Abschluß dieser Untersuchung verfügen wir nun über Daten von 297 Patientinnen und 580 Kontrollpersonen.

In der vorliegenden Arbeit werden die Rauchgewohnheiten der Patientinnen und Kontrollpersonen analysiert, wobei mittels einer neuen Methode (17) die Rauchkondensat-Expositionen (Teer-Exposition) der Zigarettenraucher quantitativ bestimmt wird.

Patientengut und Methodik

In einer Fall-Kontroll-Studie wurden in den Jahren 1977 bis Anfang 1980 insgesamt 297 weibliche Patienten mit histologisch verifiziertem Lungenkrebs mittels eines standardisierten Fragebogens (1) interviewt. Die Untersuchung wurde überregional in 15 Zentren, die sich mit der Diagnose und Therapie des Bronchuskarzinoms befassen, durchgeführt. Die Interviews wurden zum Zeitpunkt der Diagnosestellung erhoben. Als Kontrollpersonen wurden in den Erhebungszentren bzw. in der Wohnumgebung der Patientinnen 580 altersmäßig entsprechende (±2 Jahre) Personen interviewt, die zum Zeitpunkt der Befragung nicht wegen einer tabakassoziierten Krankheit (1) in Behandlung gestanden haben. Ausschlußdiagnosen waren: Krebs der Mundhöhle, Speiseröhre, oberen Luftwege, Kehlkopf, Bauchspeicheldrüse, Harnblase und Niere; Herzinfarkt, Aneurysma der Aorta, arterielle

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Durchblutungsstörungen, Emphysem, chronische Bronchitis, Magen-Zwölffingerdarmgeschwür, Leberzirrhose, Schlaganfall.

Die einzelnen histologischen Typen des Bronchuskarzinoms wurden in den Gruppen (8) Kreyberg I und Kreyberg II zusammengefaßt.

Bei den Raucherinnen wurden neben dem gegenwärtigen Rauchstatus folgende weitere Aspekte berücksichtigt:

- Alter bei Beginn der Rauchgewohnheit
- Gesamtrauchdauer in Jahren
- Dauer der Abstinenz
- Alle jemals geauchten Zigarettenmarken einschließlich jeweiliger Menge und Dauer des Konsums.

Die angegebenen Zigarettensorten wurden entsprechend ihrem Teergehalt (2) einer von drei möglichen Markengruppen zugeordnet (9). Gruppe I: < 15 mg/Zig.; Gruppe II: 15 bis 24 mg/Zig.; Gruppe III > 24 mg/Zig.

Aufgrund der Angaben über Menge, Konsumdauer und Schadstoffgehalt aller jemals konsumierten Zigaretten wurde der Teer-Expositionswert (= TEW) nach folgender Formel berechnet (17):

$$TEW = \sum_{i,j=1}^{n} (a_{xi}\, b_{xj})\, k_x + \sum_{i,j=1}^{n} (a_{yi}\, b_{yj})\, k_y + \sum_{i,j=1}^{n} (a_{zi}\, b_{zj})\, k_z$$

a_x, a_y, a_z = Zigarettenkonsum/Tag, Gruppen I, II, III
b_x, b_y, b_z = Zigarettenkonsum-Dauer/Jahre, Gruppen I, II, III
k_x, k_y, k_z = konstanter Faktor für Gruppen I, II, III (= 1, 2, 3)

Von den Daten wurden Strata für die Altersgruppen „unter 40 Jahre", „41 bis 50 Jahre", „51 bis 60 Jahre", „61 bis 70 Jahre" und „über 70 Jahre" sowie für die TEW-Bereiche „unter 500", „501 bis 1000", „100 bis 2000", „2001 bis 3000", „3001 und darüber" gebildet. Die Berechnung des Risikos (13) erfolgte für die einzelnen Altersgruppen nach Adjustierung des TEW und für einzelne TEW-Bereiche nach Adjustierung des Alters sowie nach Adjustierung von Alter und TEW für Frauen, die vor dem 19. Lebensjahr bzw. danach begonnen haben Zigaretten zu rauchen. Es wurden die 95% Konfidenzgrenzen (14) berechnet und die einzelnen Strata auf Homogenität geprüft. Es wurde der Anteil der Krankheitsfälle bei Exponierten einzelner TEW-Stufen, der durch Zigarettenrauchen erklärt werden kann (attributable risk), berechnet (3). Weiters wurde für die einzelnen Altersklassen der maximale Anteil der Krankheitsfälle, der dem Rauchen zuzuschreiben ist (population attributable risk), berechnet (12). Die Berechnung des Lungenkrebsrisikos der Ex-Raucherinnen in Relation zur Dauer der Abstinenz erfolgte ohne Adjustierung von Alter und TEW.

Ergebnisse

Von den 297 Patientinnen hatten 202 (68%) einen Tumor der Gruppe Kreyberg I und 95 Patientinnen einen Tumor der Gruppe Kreyberg II.

Der Rauchstatus der Patientinnen und der Kontrollpersonen zum Zeitpunkt der Befragung ist in Tab. 1 wiedergegeben. Es wurden ausschließlich Zigaretten konsumiert.

Signifikant (= sig.) mehr Raucherinnen als in der Kontrollgruppe finden sich in folgenden Patientengruppen:

- Alle Patientinnen (X^2 156,14; P < 1%)
- Patientinnen mit einem Tumor der Gruppe Kreyberg I (X^2 225,76; P < 1%)

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Tabelle 1. Rauchstatus weiblicher Bronchuskarzinom-Patienten (Gruppen Kreyberg I und Kreyberg II) und Kontrollpersonen

Table 1. Smoking status of female lung cancer cases (groups Kreyberg I and II) and controls

	Alle Karzinome		Kreyberg I		Kreyberg II		Kontrollen	
	n	%	n	%	n	%	n	%
Zigaretten-Raucher	188*	63	161*	80	27**	28	119	21
(Ex-Raucher)	(62)		(50)		(12)		(51)	
Niemals-Raucher	109	37	41	20	68	72	461	79
Summe	297	100	202	100	95	100	580	100

* Alle Karzinome, K I:Ko; $P < 1\%$.
** K I:K II; $P < 1\%$.

Patientinnen mit einem Tumor der Gruppe Kreyberg I haben sig. häufiger (X^2 70,95; $P < 1\%$) geraucht als Patientinnen mit einem Tumor der Gruppe Kreyberg II.

In Tab. 2 ist das Durchschnittsalter, das Durchschnittsalter bei Aufnahme der Rauchgewohnheit, die durchschnittliche Konsumdauer und der durchschnittliche Teer-Expositionswert für Patientinnen und Kontrollpersonen, die geraucht haben, dargestellt.

Tabelle 2. Weibliche Bronchuskarzinom-Patienten (Gruppen Kreyberg I und Kreyberg II) und Kontrollpersonen, Alter, Alter bei Rauchbeginn, Rauchdauer und Teer-Expositionswert (SF)

Table 2. Female lung cancer cases (groups Kreyberg I and II) and controls, age at diagnosis, age at commencement of smoking, duration of smoking habit in years and tar exposure (SE)

ø	Alle Karzinome (n = 188)		Kreyberg I (n = 161)		Kreyberg II (n = 27)		Kontrollen (n = 119)	
Alter zum Diagnosezeitpunkt	64,3	(0,77)	64,2	(0,84)	64,8	(2,02)	63,1	(1,08)
Alter bei Rauchbeginn	23,2	(0,53)	23,1	(0,88)	23,8	(1,14)	24,6	(0,59)
Jahre geraucht	39,3*	(0,83)	39,6*	(0,89)	37,4	(2,30)	31,9	(1,35)
Teer-Expositionswert	1767*	(77)	1810*	(84)	1508	(191)	1146	(122)

* $P < 1\%$.

Sig. länger als Kontrollpersonen haben geraucht:
- Alle Patientinnen ($t = 4,92$; $P < 1\%$)
- Patientinnen mit einem Tumor der Gruppe Kreyberg I ($t = 4,96$; $P < 1\%$).

Sig. höhere Teer-Expositionswerte als Kontrollpersonen haben:
- Alle Patientinnen ($t = 4,52$; $P < 1\%$)
- Patientinnen mit einem Tumor der Gruppe Kreyberg I ($t = 4,63$; $P < 1\%$).

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Tabelle 3. Weibliche Zigarettenraucher, Lungenkrebsrisiko (adj. für Teer-Expositionswerte) in Relation zum Alter (Niemals-Rauchertinnen R = 1,0) und „population attributable risk" (PAR)

Table 3. Female smokers, lung cancer risk (adjusted for tar exposure) in relation to age (never smoked R = 1,0) and population attributable risk (PAR)

	Altersgruppen										insgesamt	
	< 40		41–50		51–60		61–70		> 71			
	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
Patientinnen (n)	4	4	14	11	42	17	68	41	60	36	188	109
Kontrollen (n)	8	8	11	37	31	98	41	189	28	129	119	461
R		1,1		4,2		7,6		7,8		8,0		7,3
95% Vertrauensbereich		0,2–5,4		1,8–9,7		4,7–12,4		5,3–11,4		5,1–12,4		5,0–9,0
X^2		0,09		9,94*		64,66*		109,46*		82,42*		160,79*
X^2_{1-4} Homogenität	X^2_1 0,01		X^2_1 5,97		X^2_1 9,31		X^2_1 4,59		X^2_1 2,83		X^2_1 6,14	
PAR		3%		42%		62%		54%		55%		54%

* $P < 1\%$; R = Raucher, NR = Niemals-Raucher

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Tabelle 4. Weibliche Zigarettenraucher, Lungenkrebsrisiko (adjustiert nach Alter) in Relation zur Höhe der Teer-Exposition (Niemals-Raucherinnen R = 1,0), alle Karzinome, Gruppen Kreyberg I und Kreyberg II sowie „attributable risk" (AR)

Table 4. Female smokers, lung cancer risk (adjusted for age) in relation to tar exposure (never smoked R = 1,0), all cases, groups Kreyberg I and Kreyberg II and attributable risk (AR)

Raucher (n)	Teer-Exposition				
	< 500	501–1000	1001–2000	2001–3000	> 3001
Patientinnen (K I + K II)	12	30	81	47	18
Kontrollen	34	32	29	18	6
R	1,5	4,2	12,1	11,1	13,0
95% Vertrauensbereich	0,6–3,6	2,5–7,2	7,8–18,9	6,4–18,4	6,0–28,4
X^2	0,60	27,04*	119,03*	84,38*	38,19*
X^2_{n-1} Homogenität	X^2_3 1,60	X^2_4 1,89	X^2_4 2,62	X^2_3 1,30	X^2_3 0,34
AR	34%	76%	92%	91%	92%
Kreyberg I	8	25	70	42	16
R	2,9	9,9	27,2	25,2	29,7
95% Vertrauensbereich	0,1–105,5	5,6–17,2	17,8–43,1	15,1–41,8	14,0–60,1
X^2	0,25	61,09*	211,97*	149,33*	75,28*
X^2_{n-1} Homogenität	X^2_4 1,17	X^2_4 1,92	X^2_3 3,01	X^2_3 2,06	X^2_3 0,15
Kreyberg II	4	5	11	5	2
R	0,8	1,1	2,6	2,0	3,3
95% Vertrauensbereich	0,3–2,1	0,4–2,9	1,2–5,4	0,7–5,4	0,3–> 100
X^2	0,50	< 0,01	5,31**	0,94	< 0,01
X^2_{n-1} Homogenität	X^2_4 1,34	X^2_4 2,33	X^2_3 1,29	X^2_3 2,05	X^2_3 1,00

* $P < 1\%$, ** $P < 5\%$

Patientinnen, die niemals geraucht haben, waren zum Zeitpunkt der Diagnose durchschnittlich 63,7 Jahre (SF = 1,1) alt; Kreyberg I: 61,9 Jahre (SF = 3,1), Kreyberg II: 65,5 Jahre (SF = 2,2). Die Niemals-Raucherinnen unter den Kontrollpersonen waren zum Zeitpunkt der Befragung durchschnittlich 63,7 Jahre (SF = 0,9) alt.

Von den 188 Patientinnen (Kreyberg I: 161; Kreyberg II: 27), die Zigaretten geraucht haben, waren 62 (33%) zum Zeitpunkt der Befragung Ex-Raucherinnen (Kreyberg I: 31%; Kreyberg II: 44%).

Von den 119 Kontrollpersonen, die geraucht haben, waren 51 (43%) Ex-Raucherinnen.

Die durchschnittliche Dauer der Abstinenz betrug für alle Patientinnen 5,3 Jahre (SF = 0,9); Patientinnen mit einem Tumor der Gruppe Kreyberg I 4,8 Jahre (SF = 0,9); Patientinnen mit einem Kreyberg II Tumor 7,3 Jahre (SF = 2,3); Kontrollpersonen 11,9 Jahre (SF = 1,4). Alle Patientinnen sowie Patientinnen mit einem Tumor der Gruppe Kreyberg I, die das Rauchen eingestellt haben, waren sig. kürzer abstinent ($t = 3,97$; $P < 1\%$; $t = 4,02$; $P < 1\%$) als die Ex-Raucherinnen in der Kontrollgruppe.

Von den 62 Patientinnen (51 Kontrollpersonen), die zu Rauchen aufgehört haben, gaben als Grund an: 3% (7%) Husten, 77% (53%) andere Gesundheitsgründe, 20% (40%) Gründe, die nicht mit der Gesundheit in Zusammenhang stehen.

Das Lungenkrebsrisiko weiblicher Ex-Raucherinnen gegenüber Frauen, die niemals geraucht haben (R = 1,0), beträgt für eine Dauer der Abstinenz von: 1–4 Jahre R = 12,8, X^2 78,95, $P < 1\%$; 5–9 Jahre R = 7,1, X^2 14,24, $P < 1\%$; 10–19 Jahre R = 1,6; 20–29 Jahre R = 2,1; > 30 Jahre und darüber R = 1,9.

In Tab. 3 ist das Lungenkrebsrisiko (adjustiert nach TEW) für einzelne Altersgruppen sowie der maximale Anteil der Krankheitsfälle, der in diesen Altersklassen dem Rauchen zuzuschreiben ist (population attributable risk) wiedergegeben. Raucherinnen haben ab dem 40. Lebensjahr gegenüber Frauen, die nicht rauchen, ein sig. erhöhtes Lungenkrebsrisiko ($P < 1\%$).

In Tab. 4 ist das Lungenkrebsrisiko weiblicher Zigarettenraucherinnen (adjustiert nach Alter) in Abhängigkeit zur Höhe der Teer-Exposition sowie der Anteil der Krankheitsfälle bei Exponierten einzelner TEW-Stufen, der durch Zigarettenrauchen erklärt werden kann, dargestellt.

Raucherinnen weisen eine sig. Zunahme ($P < 1\%$) des Lungenkrebsrisikos ab einer Teer-Exposition von mehr als 501 auf. Dies trifft für die Tumoren der Gruppe Kreyberg I zu. Gegenüber den Tumoren der Gruppe Kreyberg II konnte nur im Bereich 1001 bis 2000 eine sig. Zunahme ($P < 5\%$ des Erkrankungsrisikos nachgewiesen werden.

Frauen, die vor dem 19. Lebensjahr zu rauchen begonnen haben, weisen gegenüber Niemals-Raucherinnen ein Lungenkrebsrisiko (adjustiert für Alter und TEW) von R = 7,8 (95% Vertrauensbereich: 5,2–11,6; X^2 90,65, $P < 1\%$) auf. Wurde nach dem 19. Lebensjahr mit dem Zigarettenkonsum begonnen, beträgt das Erkrankungsrisiko R = 6,5 (95% Vertrauensbereich: 5,0–8,4; X^2 198,31, $P < 1\%$).

Diskussion

Entsprechend der ätiologischen Bedeutung des Zigarettenrauchens für das Entstehen von Lungenkrebs finden sich unter den Patientinnen sig. mehr Raucherinnen als in der Kontrollgruppe. Dies trifft vor allem für Frauen mit einem Tumor der

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Gruppe Kreyberg I zu, die in unserem Patientengut mit 68% den überwiegenden Anteil der histologischen Typen stellen. Verglichen mit der Kontrollgruppe weisen die Raucher unter den Patientinnen ein extremes Konsumverhalten auf. Dies zeigt sich deutlich an den sig. Unterschieden bei den einzelnen Bewertungsgrößen der Rauchgewohnheit. Der höhere Teer-Expositionswert (TEW) der Patientinnen wird neben der längeren Konsumgewohnheit vor allem dadurch bestimmt, daß sie sig. häufiger sowie täglich mehr schadstoffreiche Zigaretten der Gruppe III (> 24 mg/Zig.) konsumiert haben als Kontrollpersonen (15, 17).

Das Einstellen der Rauchgewohnheit führt nach einem kurzzeitigen Ansteigen zu einer deutlichen Abnahme des Erkrankungsrisikos, ohne jedoch jemals das Risiko einer Niemals-Raucherin zu erreichen. Entsprechend der kürzeren Dauer der Abstinenz geben die Ex-Raucherinnen unter den Patientinnen häufiger Gesundheitsgründe (80%) als Ursache des Einstellens der Rauchgewohnheit an als jene in der Kontrollgruppe (60%).

Da im TEW die Zahl der täglich gerauchten Zigaretten, die Konsumdauer und der Schadstoffgehalt aller jemals konsumierten Zigarettensorten mitberücksichtigt sind, läßt sich mit dem TEW das Lungenkrebsrisiko exakter bestimmen, als mit den bisherigen Verfahren, die meist nur die Gesamtzahl der konsumierten Zigaretten oder die Dauer der Rauchgewohnheit berücksichtigen und daher weniger ausgeprägte Ergebnisse erzielen (16). Das Lungenkrebsrisiko nimmt mit steigendem TEW zu. Dies trifft für die Kreyberg I Tumore zu; hingegen zeigt das erhöhte Risiko gegenüber den Kreyberg II Tumoren keine ausgeprägte Dosis-Wirkungs-Beziehung.

Die Zunahme des Erkrankungsrisikos mit dem Alter steht mit der Risikozunahme bei steigendem TEW in Beziehung. Der Anteil der Lungenkrebsfälle, der dem Zigarettenrauchen zuzuschreiben ist (population attributable risk = PAR), erreicht in der Altersgruppe 51 bis 60 Jahre mit 62% seinen höchsten Wert. Trotz einer hohen Zahl von Exponierten ist das PAR bei den unter 40jährigen Frauen gering, da die Raucherinnen in diesem Altersbereich wegen der noch geringen Schadstoffbelastung (niedriger TEW) keine ausgeprägte Zunahme des Erkrankungsrisikos aufweisen. Das geringe Absinken des PAR bei den über 60jährigen Frauen ist auf die kleine Zahl der Raucherinnen in diesem Altersbereich zurückzuführen; kompensierend wirkt hier das wegen der hohen Schadstoffbelastung (hoher TEW) große Erkrankungsrisiko der Raucherinnen.

Die Berechnung des Risikos ermöglicht es, den „kritischen Bereich" der Schadstoffbelastung zu bestimmen, ab dem das Lungenkrebsrisiko des Rauchers sig. ansteigt. Aufgrund der Ergebnisse (unter besonderer Berücksichtigung der Kreyberg I Tumoren, die eine deutlich ausgeprägte Dosis-Wirkungs-Beziehung aufweisen) ist der „kritische Bereich" der Schadstoffbelastung in der Größenordnung um TEW = 500 festzusetzen. Entsprechend steigt der Anteil der Krankheitsfälle unter den Rauchern, der durch Zigarettenrauchen erklärt werden kann (attributable risk), ab dem TEW-Bereich von über 500 drastisch an. Übereinstimmende Ergebnisse fanden wir bei männlichen Rauchern (11, 17). Bestimmungen des „kritischen Bereichs" der Schadstoffbelastung bei Zigarettenrauchern sind im Zusammenhang mit der Diskussion um die sogenannte „less hazardous cigarette" (5) von Bedeutung. Die Produktmodifikation (Absenkung des Kondensatgehaltes der Zigaretten) sollte auch bei Personen mit extremen Rauchverhalten (= Hochrisikogruppe für Lungenkrebs) zu einer Senkung des Lungenkrebsrisikos führen, vorausgesetzt, es erfolgt keine Kompensation durch Verlängerung der Konsumgewohnheit und/oder Zunahme der Zahl der täglich gerauchten Zigaretten.

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Das Erkrankungsrisiko eines Rauchers wird vom Alter bei Aufnahme der Konsumgewohnheit mit bestimmt (6, 7). In unserem Untersuchungsgut weisen Frauen, die vor dem Erreichen des 19. Lebensjahrs mit dem Rauchen begonnen haben, gegenüber Niemals-Raucherinnen ein höheres Lungenkrebsrisiko (adjustiert für Alter und TEW) auf als Frauen, die nach dem 19. Lebensjahr begonnen haben.

Da Frauen immer früher im jugendlichen Alter mit dem Rauchen beginnen und der tägliche Zigarettenkonsum ansteigt (18) – von 1972 bis 1979 hat sich der Anteil der Frauen, die mehr als 20 Zigaretten täglich rauchen, verdoppelt (4) – muß in Zukunft, trotz Abnahme des durchschnittlichen Schadstoffgehaltes der Zigaretten (18), mit einem Ansteigen des Erkrankungsrisikos bei weiblichen Rauchern gerechnet werden.

Dies wird sich auch in einer Risikozunahme bei den unter 40jährigen Tabakkonsumentinnen bemerkbar machen, für die in der vorliegenden Studie noch kein Ansteigen des Risikos festgestellt werden konnte. Aufgrund dieser Risikozunahme bei weiblichen Tabakkonsumenten und der zunehmenden Verbreitung der Rauchgewohnheit bei weiblichen Jugendlichen (18) wird in Österreich die Inzidenz des Bronchuskarzinoms bei Frauen weiter ansteigen.

Die Prioritäten der Prävention des tabak-assoziierten Bronchuskarzinoms (und aller tabakassoziierten Erkrankungen) liegen in der Erhaltung der Tabakabstinenz von Niemals-Rauchern und in der Entwöhnung von Rauchern. Die vorliegende Untersuchung zeigt die Notwendigkeit auf, Frauen (vor allem Jugendliche) verstärkt in entsprechenden Interventionsmaßnahmen (10) als eigene Zielgruppe zu berücksichtigen, um einer drastischen Ausweitung der Lungenkrebs-Epidemie (bzw. tabakassoziierter Erkrankungen) bei Frauen vorzubeugen.

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Scanning Electron Microscopical Investigations on the Respiratory Epithelium of the Syrian Golden Hamster
V. Dose-Related in vitro Effects of Benzo(a)pyrene[1]

Rasterelektronenmikroskopische Untersuchungen des Respirationsepithels vom Syrischen Goldhamster
V. Dosisbedingter Effekt von Benzo(a)pyren in vitro[1]

HANS-BERNHARD RICHTER-REICHHELM, MAKITO EMURA, and JÜRGEN ALTHOFF[2]

With 10 Figures

Abstract

The biological effects of *in vitro* exposure of fetal hamster tracheal explants to three dose levels of benzo(a)pyrene (BaP: 25, 50, 100 µg/ml medium) in 0.5% dimethylsulphoxide (DMSO) were studied by light and scanning electron microscopy. A dose-related difference was seen in the quality of the observed pathological alterations in the specimens examined after 28 days of culture. Whilst in the explants treated with 50 or 100 µg/ml BaP the respiratory epithelium revealed necrotic areas and extended metaplastic alterations, explants exposed to 25 µg/ml BaP showed normal differentiation in some areas of the respiratory epithelium. In explants treated with the highest dose (100 µg/ml BaP), hyperplastic foci were seen in the epithelium and tended to proliferate towards the tracheal lumen. These observations show similarity with early neoplastic alterations.

Zusammenfassung

Die biologische Wirksamkeit von 3 Benzo(a)pyrendosierungen (BaP: 25, 50 und 100 µg/ml Medium) gelöst in 0,5% Dimethylsulfoxid (DMSO) wurde nach *in vitro* Exposition an

[1] Inventory and Biological Impact of Polycyclic Carcinogens in the Environment, Part 19.

[2] The present studies were carried out in accordance with the environmental plan of the Federal Environment Office by the order of the Federal Ministry of the Interior. We are grateful to *G. Schoch, D. Kracke, H. Peesel* and *B. Alsen* for excellent technical assistance and to *S. Hamilton* for help with the manuscript.

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AUERBACH, O.

"CIGARETTE SMOKING AND LUNG CANCER (AN OVERVIEW)"

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Lung Cancer:

Causes and Prevention

Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983

Edited by

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CHAPTER 14

Lung Cancer in Japan: Effects of Nutrition and Passive Smoking

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ABSTRACT

Lung cancer is on a sharp increase in both men and women in Japan. Nonsmoking wives with smoking husbands were found to carry an elevated risk of lung cancer and ischemic heart disease by a large-scale cohort study, 1966-1981, for 265,118 adults in 29 Health Center Districts in Japan, the risk steadily going up with the increase in number of cigarettes smoked by the husband. In major cancers other than lung, no such risk elevation was observed. A nonsmoking husband with a smoking wife also showed an elevated risk of lung cancer. The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking just as for active smoking. Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking. Such risk reduction was not observed for ischemic heart disease. The observed results suggest that the influence of husband's smoking on nonsmoking wives in raising the risk of lung cancer is as a cancer promoter rather than a cancer initiator. This promoter hypothesis may explain why such continuous but low-dose exposure of passive smoking, which starts after adult age is reached, significantly elevates lung cancer risk in nonsmoking wives.

Key Words: **Japan, cohort study, passive smoking, lung cancer, ischemic heart disease, green-yellow vegetables, β-carotene, promoter, promoter-inhibitor**

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Lung Cancer: Causes and Prevention.

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Introduction

The mortality from lung cancer has been increasing rapidly in Japan (Figure 1). The number of deaths among males was 520 in 1947 and 17,555 in 1982, the corresponding number for females was 248 and 6661.

There exists little sign of a slowing down of the rate of increase, and the number of deaths from lung cancer are expected to exceed the number of deaths from stomach cancer in the near future. In parallel to this trend the number of cigarettes sold in Japan also has been on a sharp rise (Figure 1). The random sample survey conducted by the Tobacco Monopoly Corporation in 1982 revealed that currently 70.1% of adult males and 15.4% of adult females smoke in Japan.

The purpose of this chapter is to study the causative factors of lung cancer in Japan with special reference to the effect of passive smoking relative to the effect of active smoking. The possible influence of nutrition, β-carotene-rich green-yellow vegetables in particular, on the risk enhancing effect of active and passive smoking also is studied.

Methods

The materials of our ongoing large-scale cohort study for 265,118 adults aged 40 years and above in Japan were analyzed in detail to discover factors altering the

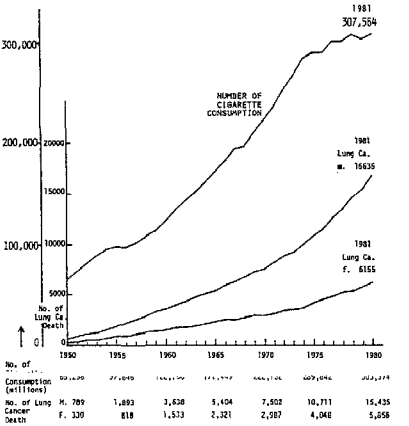

Figure 1. Trends in cigarette consumption and lung cancer deaths in Japan (1950–1981).

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risk of lung cancer in both men and women. For statistical analysis, programs included in the book *Epidemiologic Analysis with a Programmable Calculator* (U.S. Department of Health, Education and Welfare, 1979) mainly were used.

Results

Active Smoking and Lung Cancer Risk

Cigarette smoking was identified by far the most important cause of lung cancer in Japan, both by case-control studies conducted by the author and other researchers and by a large-scale cohort study (1–6) being conducted by the author for 265,118 adults (122,261 men and 142,857 women) aged 40 and above (95% of census population) in 29 Health Center Districts in Japan. These subjects were surveyed in October–December 1965 and followed up from January 1966 until December 1981. A clear-cut dose-response relationship was observed between the number of cigarettes ever smoked and the age-standardized mortality rate of lung cancer. The mortality rate of lung cancer also was found to be higher the earlier smoking was begun when age and total number of cigarettes ever smoked were standardized (Figure 2). The lung cancer-standardized mortality rate was observed

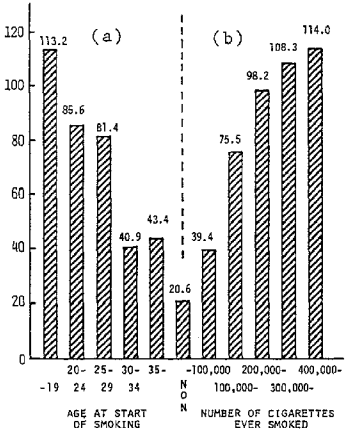

Figure 2. Lung Cancer. (a) Attained age- and amount of smoking-standardized mortality rate by age at start of smoking. (b) Attained age- and age at start of smoking-standardized mortality rate by total amount of cigarettes ever smoked. (Prospective study, 1966–1978 Japan.)

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to be 18.3% lower in smokers who do not inhale compared to regular deep inhalers, and 48.9% lower in smokers of filtertip cigarettes compared to smokers of nonfiltertip cigarettes, according to our cohort study. The risk of lung cancer in daily smokers also was noted to approach gradually that of nonsmokers with the lapse of years after smoking cessation, risk difference diminishing by 41.6% in 5 years after stopping the habit. This strongly suggests the major part of the influence of smoking during adulthood is the promoter action of substances included in mainstream smoke.

Effect of Nutrition on Active Smokers

Daily intake of green-yellow vegetables, rich in β-carotene, was found significantly to lower the risk of lung cancer (7, 8), particularly when the total amount of cigarettes ever smoked was less than 300,000 (6) (Figure 3). No other dietary habit showed such risk reduction. Risk reduction after smoking cessation appeared to be more pronounced in case of daily consumers of green-yellow vegetables. Taking similar evidence in laboratory studies into consideration, a promoter-inhibitor interaction model was conceptualized.

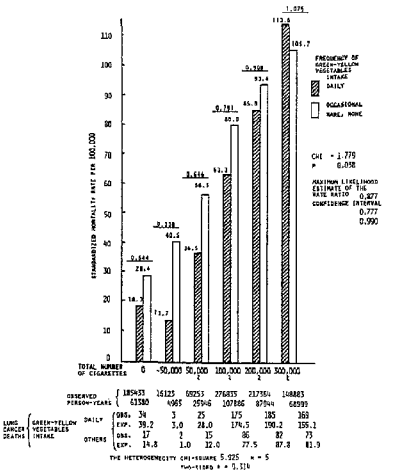

Figure 3. Standardized mortality rate for lung cancer by total number of cigarettes ever smoked and by frequency of green-yellow vegetable intake; males. (Prospective study, 1966-1978.)

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Figure 4. Age-
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Passive Smoking and Lung Cancer

In the present cohort study (1966–1981), 427 deaths from lung cancer in women were recorded during 16 years of followup (1966–1981). Of these women, 269 were married, and 200 of these also were nonsmokers. These cases occurred among 91,540 nonsmoking married women whose husbands' smoking habits were studied. The risk of lung cancer was carefully measured, taking into consideration possible confounding variables. There was a statistically significant increased risk in relation to the extent of the husband's smoking (Figure 4), which confirmed the validity of previous reports (9, 10). The association was significant when observed by age of husbands (Table 1, Figures 1 and 5) and also by age of wives (Table 2). The further detailed analysis on materials cross-tabulated by age and occupation of the husband also confirmed the association (Table 3). The husband's drinking habits were noted to have no effect in raising the risk of lung cancer in nonsmoking wives (Table 4).

Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking also was observed with ischemic heart disease when observed by husband's age and occupation (Tables 5 and 6). The significant risk elevation of cancer of the nasal sinus also was observed in nonsmoking wives with husband's smoking. The risk elevation of emphysema and chronic bronchitis with spouse's smoking also was noted with borderline significance. However there was no tendency of risk elevation at all in major cancers other than lung (total of cancers of stomach, cervix, and breast), the standardized mortality rate in nonsmoking wives being almost exactly the same regardless of the husband's smoking habit (Table 7, Figure 6).

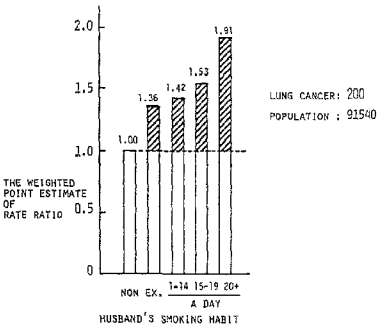

Figure 4. Age-standardized mortality rate ratio for lung cancer in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Table 1. Mortality rate for lung cancer in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966-1981, Japan[a]

Husband's age group	Husband's smoking habit: Nonsmoker No.	Pop.	Ex-smoker No.	Pop.	Number of cigarettes a day: 1-14/d No.	Pop.	15-19/d No.	Pop.	20+/d No.	Pop.	Total No.	Pop.
40-49	4	6,229	1	1,255	8	8,621	6	5,158	16	10,764	35	32,027
50-59	10	7,791	3	1,922	20	9,668	8	4,052	24	9,820	65	33,253
60-69	18	7,120	11	2,687	28	7,243	9	2,513	23	4,651	89	24,214
70-79	5	755	2	348	2	612	1	105	1	226	11	2,046
Total	37	21,895	17	6,212	58	26,144	24	11,828	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.36	2.18 0.85	1.42	2.01 1.01 2.02	1.38	2.38 0.98	1.91	2.71 1.34	Mantel extension χ^2 2.915 one-tail p value 0.00178	
Mantel-Haenszel χ^2 one-tail p value	—			1.0855 0.1389		1.45 1.8290 0.0337		1.04 3.0295 0.0012				

Table 2. Mortality rate for lung cancer in nonsmoking wives by smoking habit of husbands and by age group of wife: prospective study; 1966-1981, Japan[a]

Wife's age group	Husband's smoking habit: Nonsmoker No.	Pop.	Number of cigarettes a day: Ex-smoker 1-19/d No.	Pop.	20+/d No.	Pop.	Total No.	Pop.
40-49	4	7,918	21	17,492	21	12,615	46	38,025
50-59	14	7,635	46	15,640	31	8,814	91	32,089
60-69	16	6,170	31	10,361	10	3,793	57	20,344
70-79	3	172	1	671	2	239	6	1,082
Total	37	21,895	99	44,184	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00			2.01 0.99		2.55 1.19	Mantel extension χ^2 2.424 one-tail p value 0.00768	
Mantel-Haenszel χ^2 one-tail p value	—			1.6042 0.0543		2.3731 0.0088		

Table 3. Mo
of husbands

Husbands age (year)
40-49
50-59
60-69
70 +

[a]Standardized Risk Ratios

[b]Occupation: 1. sales workers; 5 in transport and workers; 10, no

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 3. Mortality rate for lung cancer in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)[a]

Husbands age (year)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	4	6,229	15	15,034	16	10,764
	1		324		653	1	566
	2		90		231		293
	3	1	908	2	2,247	3	1,867
	4	1	476	1	993		1,044
	5	1	2,502	6	5,941	9	3,636
	6		46		165		108
	7		177	1	486	1	426
	8		1,112	3	3,431	2	2,241
	9		162	1	345		243
	10	1	432	1	542		340
50–59	Total	10	7,791	31	15,642	24	9,820
	1	1	345		593	2	446
	2		175		253	1	319
	3	1	817	5	1,764	1	1,324
	4	1	653	2	1,133	5	1,092
	5	4	3,497	16	6,812	9	3,514
	6		35		89		50
	7		120		273	1	234
	8	3	1,375	6	3,478	2	2,155
	9		164		378	1	251
	10		610	2	869	2	435
60–69	Total	18	7,120	48	12,443	23	4,651
	1		227	1	327	1	179
	2	1	91		143		124
	3		305	2	594	2	327
	4	2	508	5	822	1	500
	5	13	4,084	33	6,845	10	2,152
	6		9		31		14
	7		45		82		55
	8	1	805	5	1,784	4	736
	9		121	1	208		92
	10	1	925	1	1,507	5	472
70 +	Total	5	755	5	1,065	1	226
	1		32		30		5
	2		21		14		4
	3		18	1	36		8
	4		48		73		20
	5	3	323	1	446		89
	6		1		1		0
	7		1		5		1
	8		87	2	119	1	36
	9		11		19		2
	10	2	213	1	322		61
[a] Standardized Risk Ratios		1.000		1.436		1.872	

Mantel extension χ^2: 3.124; one-tail p value: 0.00089.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

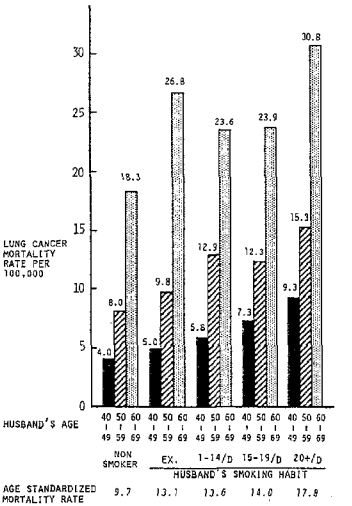

Figure 5. Age-specific mortality rate for lung cancer per 100,000 in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

Table 4. Mortality rate for lung cancer in women by age group and by alcohol drinking habits of husband: (patient herself a nonsmoker); prospective study, 1966–1981, Japan

Husband's age group	Husband's drinking habits: Nondrinker No.	Nondrinker Pop.	Occas. Rare No.	Occas. Rare Pop.	Daily No.	Daily Pop.	Obscure No.	Obscure Pop.	Total No.	Total Pop.
40–49	12	6,141	10	15,877	13	9,935	0	74	35	32,027
50–59	12	7,437	29	14,666	24	10,786	0	364	65	33,253
60–69	23	6,741	35	9,234	27	7,606	4	633	89	24,214
70–79	1	686	5	666	4	589	1	105	11	2,046
Total	48	21,005	79	40,443	68	28,916	5	1,176	200	91,540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00			1.61 0.66		1.59 0.77				
Mantel-Haenszel χ^2 one-tail p value	—			=0.1019 0.1594		0.4564 0.3240			Mantel extension χ^2 0.626 one-tail p value	0.26566

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 5. Mortality rate for ischemic heart diseases in women by age group and by smoking habits of husband: prospective study, 1966–1981, Japan

Husband's age group	Husband's smoking habit: Nonsmoker No.	Nonsmoker Pop.	Ex-smoker 1-19/d No.	Ex-smoker 1-19/d Pop.	20+/d No.	20+/d Pop.	Total No.	Total Pop.
			Number of cigarettes a day					
40–49	13	6,229	40	15,034	33	10,764	86	32,027
50–59	26	7,791	56	15,642	49	9,820	131	33,253
60–69	65	7,120	125	12,443	47	4,651	237	24,214
70–79	14	755	19	1,065	7	226	40	2,046
Total	118	21,895	240	44,184	136	25,461	494	91,540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.10	1.33 0.91	1.31	1.63 1.06		
Mantel-Haenszel χ^2 one-tail p value	—		0.8504 0.1976		2.0723 0.0191		Mantel extension χ^2 2.073 one-tail p value 0.01909	

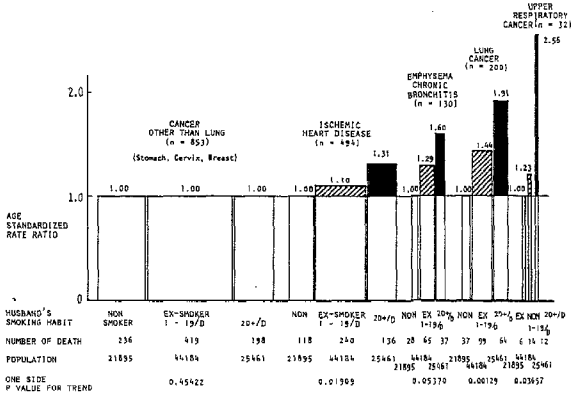

Figure 6. Standardized mortality rate ratio for selected causes of death in 91,540 nonsmoking women by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 6. Mortality rate for ischemic heart disease in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	13	6,229	40	15,034	33	10,764
	1	1	324		653	1	566
	2		90	1	231		293
	3		908	4	2,247	1	1,867
	4		476	1	993	5	1,044
	5	8	2,502	25	5,941	18	3,636
	6		46		165		108
	7	1	177	2	486		426
	8		1,112	7	3,431	6	2,241
	9		162		345	1	243
	10	3	432		542	1	340
50–59	Total	26	7,791	56	15,642	49	9,820
	1	1	345	3	593		446
	2	2	175		253		319
	3	2	817	5	1,764	6	1,324
	4		653	6	1,133	4	1,092
	5	15	3,497	27	6,812	26	3,514
	6		35	1	89		50
	7		120	1	273	2	234
	8	5	1,375	8	3,478	11	2,155
	9		164	1	378		251
	10	1	610	4	869		435
60–69	Total	65	7,120	125	12,443	47	4,651
	1	2	277	2	327	1	179
	2	1	91	2	143	1	124
	3	2	305	5	594	1	327
	4	10	508	8	822	5	500
	5	36	4,084	79	6,845	27	2,152
	6		9	1	31		14
	7	1	45	1	82	1	55
	8	7	805	13	1,784	6	736
	9	1	121	2	208		92
	10	5	925	12	1,607	5	472
70+	Total	14	755	19	1,065	7	226
	1	2	32	1	30		5
	2	2	21		14	1	4
	3		18	1	36		8
	4	1	48	1	73		20
	5	5	323	11	446	2	89
	6		1		1		0
	7		1		5		1
	8		87	1	119	3	36
	9		11	2	19		2
	10	4	213	2	322	1	61
[a] Standardized Risk Ratios		1.000		1.103		1.359	

Mantel extension χ^2: 2.351; one-tail p value: 0.00936.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

Table 7a.
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1981, Jap

Husband's age group

40–49
50–59
60–69
70–79
Total

[a] The weighte
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based 90%
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Mantel-Haer
one-tail p va

Table 7 b
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Husbands age (years)

40–49

50–59

60–69

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 7a. Mortality rates for major cancers other than lung in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966–1981, Japan[a]

Husband's age group	Husband's smoking habit (cigarettes a day)							
	Nonsmoker		Ex-smoker 1–19		20+		Total	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	44	6,229	117	15,034	71	10,764	232	32,027
50–59	97	7,791	191	15,642	119	9,820	407	33,253
60–69	160	7,120	274	12,443	106	4,651	540	24,214
70–79	14	755	20	1,065	8	226	42	2,046
Total	315	21,895	602	44,184	304	25,461	1,221	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.11 1.00 0.90		1.05 1.00 0.95		Mantel extension χ^2 0.115 one-tail p value 0.4542	
Mantel-Haenszel χ^2 one-tail p value	—		−0.0015 0.4994		0.0449 0.4821			

Table 7 b. Mortality rates for major cancers other than lung in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	45	6,229	120	15,034	74	10,764
	1	2	324	1	653	3	566
	2		90	1	231	2	293
	3	9	908	17	2,247	12	1,867
	4	3	476	8	993	8	1,044
	5	17	2,502	59	5,941	35	3,636
	6		46		165		108
	7	1	177	6	486		426
	8	10	1,112	21	3,431	13	2,241
	9	1	162	4	345	1	243
	10	2	432	3	542		340
50–59	Total	98	7,791	195	15,642	122	9,820
	1	13	345	2	593	3	446
	2	2	175	1	253	1	319
	3	14	817	16	1,764	10	1,324
	4	1	653	18	1,133	9	1,092
	5	49	3,497	81	6,812	56	3,514
	6		35		89		50
	7	2	120	4	273	2	234
	8	12	1,375	49	3,478	31	2,155
	9		164	7	378	4	251
	10	5	510	11	669	6	435
60–69	Total	161	7,120	227	12,443	106	4,651
	1	5	227	5	327	2	179
	2	5	91	3	143	3	124
	3	7	295	11	597	5	327
	4	5	508	28	822	12	500
	5	102	4,084	158	6,845	58	2,152

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 7 b. (cont.)

Husbands age (years)	Occupation[b]	Nonsmoker No.	Nonsmoker Pop.	Ex-smoker or 1–19/day No.	Ex-smoker or 1–19/day Pop.	≥20/day No.	≥20/day Pop.
	6		9	1	31		14
	7	1	45	3	82	2	55
	8	10	805	40	1,784	17	736
	9	2	121	3	208		92
	10	24	925	25	1,607	7	472
70 +	Total	14	755	21	1,065	8	226
	1		32		30		5
	2	1	21		14		4
	3	1	18		36		8
	4		48	1	73	2	20
	5	7	323	15	446	4	89
	6		1		1		0
	7		1		5		1
	8	1	87	2	119	1	36
	9		11		19		2
	10	4	213	3	322	1	61
[a] Standardized Risk Ratios		1.000		0.969		1.034	

Mantel extension χ^2: −0.129: one-tail p value: 0.44868.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

Comparison of the Effects of Active Smoking and Passive Smoking

When the risk of lung cancer in nonsmokers with nonsmoking spouses was taken as a unit, a definite dose–response relationship was observed, the highest risk being in heavy active smokers, followed by mild active smokers, then heavy passive smokers, and then mild passive smokers (Figure 7). The risk gradient was similar both in men and in women (Figure 8). A significantly elevated risk of lung cancer also was noted for nonsmoking husbands with smoking wives.

Because the size of population exposed to passive smoking is quite large in the case of women, the effect of passive smoking because of the husband's smoking was estimated as 65% of that of active smoking. Our recent survey showed that 47.5% and 32.6% of Japanese adult women were being exposed to passive smoking at home and at the workplace, respectively (Figure 9). Therefore it must be a sound estimate that the total effect of passive smoking is approximately equivalent to that of active smoking in women. However, as a majority of adult men are still smokers, the total effect of passive smoking relative to active smoking must be on

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

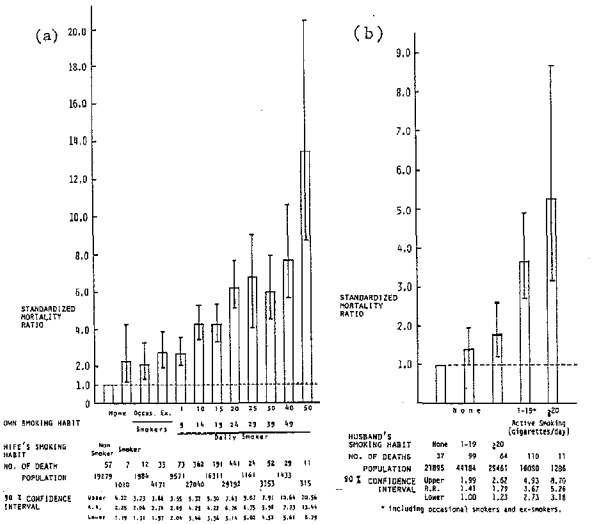

Figure 7. (a) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; males.(Prospective study, 1966–1981, Japan.) (b) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; females. (Prospective study, 1966–1981, Japan.)

the order of a few percent. The effect on lung cancer risk of passive smoking at home in relation to active smoking for men was calculated as 0.4% in our series.

Effect of Nutrition on Passive Smokers

A significantly lower risk of lung cancer was observed when nonsmoking wives with smoking husbands consumed green-yellow vegetables daily (Tables 8 and 9, Figures 10 and 11) suggesting that the promoter–inhibitor interaction model also applied to passive smoking just as in active smoking (Figure 9). Such risk reduction caused by daily intake of green–yellow vegetables was not observed for ischemic heart disease (Table 10, Figure 12).

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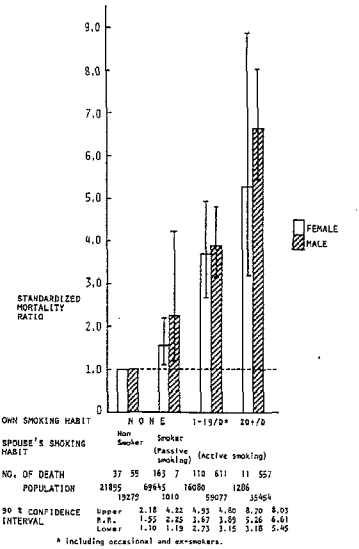

Figure 8. Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals. (Prospective study, 1966–1981, Japan.)

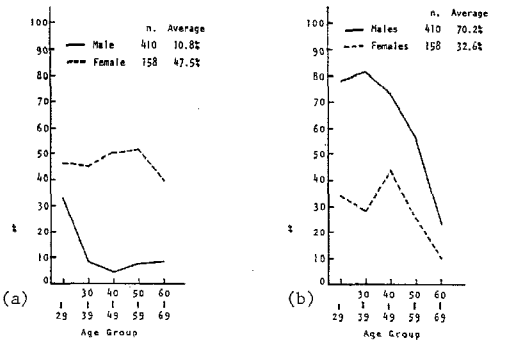

Figure 9. (a) Percentage of nonsmokers exposed to sidestream smoke at home, Japan, 1983. (b) Percentage of nonsmokers exposed to sidestream smoke at the workplace, Japan, 1983.

Table 8. Lung cancer mortality rate in nonsmoking wives by smoking habit of the husband: comparison be-

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 8. Lung cancer mortality rate in nonsmoking wives by smoking habit of the husband: comparison between daily and non daily intake of green-yellow vegetables

Husband's smoking habits		Nonsmoker				Ex-smoker on 1-19 day				≥20/day			
Wife's eating habits		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age												
Agriculture	40–49	1,958	1	544	0	5,050	5	891	1	3,037	7	599	2
	50–59	2,805	4	692	0	5,196	11	1,616	5	2,588	9	926	0
	60–69	3,359	7	725	6	5,106	22	1,739	11	1,588	6	564	4
	70–79	258	3	65	0	287	1	159	0	45	0	44	0
Others	40–49	2,422	3	1,305	0	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	3,181	5	1,113	1	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	2,266	4	770	1	4,088	9	1,510	6	1,906	10	593	3
	70–79	216	2	216	0	371	1	248	3	81	1	56	0
Total		16,465	29	5,430	8	34,118	69	10,066	30	19,255	43	6,206	21

Grand total	Population: 91540	Lung cancer: 200

Green-yellow vegetables	Mantel-extension χ^2	P-value (two tailed)
Daily	2.072	0.03827
Nondaily	2.487	0.01288
Total	3.090	0.00200

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 9. Effect of daily intake of green-yellow vegetables on lung cancer mortality in nonsmoking wives with smoking husbands[a]

Husband's smoking habit		Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green-yellow vegetables							
		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age								
Agriculture	40–49	5,050	5	891	1	3,037	7	559	2
	50–59	5,196	11	1,616	5	2,588	9	926	0
	60–69	5,106	22	1,739	11	1,588	6	564	4
	70–79	287	1	159	0	45	0	44	0
Others	40–49	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	4,088	9	1,510	6	1,906	10	593	3
	70–79	371	1	248	3	81	1	56	0
Total		34,118	69	10,066	30	19,255	43	6,206	21

[a]Mantel-Haenszel χ^2: −1,986; p (two-tailed 0.047). Odds ratio: Nondaily green-yellow vegetable intaker, 1,000; daily green-yellow vegetables intake, 0.707 (standardized rate ratio); 90% confidence limits, 0.538–0.943.

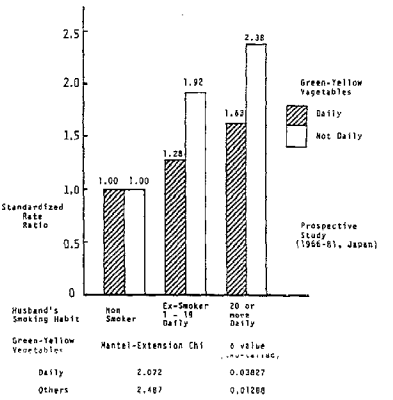

Figure 10. Lung cancer mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

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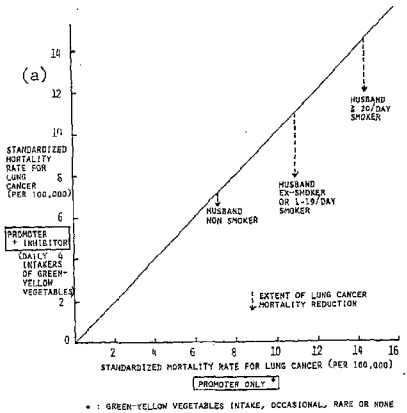
Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000


(a)
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER + INHIBITOR
(DAILY INTAKERS OF GREEN-YELLOW VEGETABLES)
HUSBAND NON SMOKER
HUSBAND EX-SMOKER OR 1-19/DAY SMOKER
HUSBAND ≥ 20/DAY SMOKER
EXTENT OF LUNG CANCER MORTALITY REDUCTION
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER ONLY*
* : GREEN-YELLOW VEGETABLES INTAKE, OCCASIONAL, RARE OR NONE

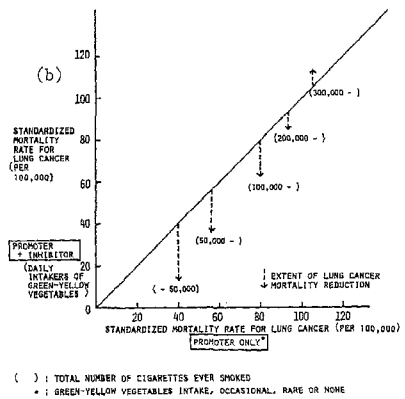

(b)
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER + INHIBITOR
(DAILY INTAKERS OF GREEN-YELLOW VEGETABLES)
(300,000 -)
(200,000 -)
(100,000 -)
(50,000 -)
(- 50,000)
EXTENT OF LUNG CANCER MORTALITY REDUCTION
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER ONLY*
( ) : TOTAL NUMBER OF CIGARETTES EVER SMOKED
* : GREEN-YELLOW VEGETABLES INTAKE, OCCASIONAL, RARE OR NONE

Figure 11. (a) Standardized mortality rate for lung cancer in nonsmoking wives by smoking habit of the husband. Comparison between daily and nondaily intake of green-yellow vegetables. (Prospective study, 1966–1981, Japan.) (b) Standardized mortality rate for lung cancer according to total number of cigarettes smoked and frequency of consumption of green-yellow vegetables; males. (Prospective study, 1966–1978, Japan.)

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Table 10. Ischemic heart disease mortality rate in nonsmoking wives by smoking habit of the husband: comparison between green-yellow vegetables intake daily and nondaily

Husband's smoking habit		Nonsmoker				Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green–yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.
Occupation	Age												
Agriculture	40–49	1,958	6	544	2	5,050	18	891	7	3,037	14	599	4
	50–59	2,805	11	692	4	5,196	25	1,616	2	2,588	21	926	5
	60–69	3,359	30	725	6	5,106	55	1,739	24	1,588	21	564	6
	70–79	258	2	65	3	287	10	159	1	45	2	44	0
Others	40–49	2,422	3	1,305	2	7,288	10	1,805	5	5,377	12	1,751	3
	50–59	3,181	8	1,113	3	6,732	18	2,098	11	4,633	17	1,673	6
	60–69	2,266	21	770	8	4,088	33	1,510	13	1,906	11	593	9
	70–79	216	7	216	2	371	6	248	2	81	3	56	2
Total		16,465	88	5,430	30	34,118	175	10,066	65	19,255	101	6,206	35
Grand total		Population: 91540				Ischemic heart disease: 494							
Green-yellow vegetables		Mantel-extension χ^2				P value (two tailed)							
Daily		2.307				0.02105							
Nondaily		0.820				0.41222							
Total		2.406				0.01613							

Figure 12. I
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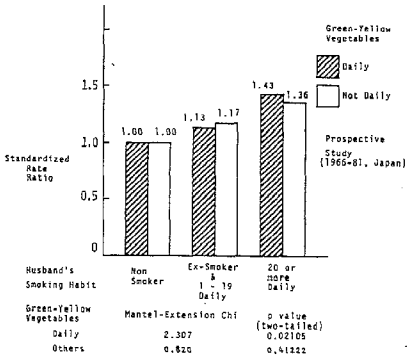

Figure 12. Ischemic heart disease mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

Discussion

The age-adjusted mortality rates for lung cancer have been sharply increasing both for men and for women in Japan. As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons for the trend of their mortality from lung cancer have been unclear. The present study appears to explain at least a part of this long-standing riddle.

This observation also questions the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing them with nonsmokers. This study shows that nonsmokers are not a homogeneous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking. Although the relative risk of indirect smoking was smaller than that of direct smoking, the absolute excess deaths from lung cancer resulting from passive smoking must be important because of the large size of the exposed group. Therefore, these results of our current study must be of public health importance, strengthening already existing evidence for a health hazard from passive smoking (11–15) (Table 11).

As shown in Figure 9, 47.5% and 32.6% of 158 nonsmoking adult women surveyed recently are noted to be exposed to sidestream smoke at home and at the workplace, respectively. One survey conducted in Aichi prefecture in Japan showed that nonsmoking wives are exposed to their husband's smoking 6.7 times a day on the average.

Because sidestream smoke contains varieties of cancer promoters at higher concentration than does mainstream smoke, it must be reasonable to consider the

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Table 11. Passive smoking is harzardous to health

1. Existence of toxic substances (including carcinogens) in sidestream smoke mostly at higher concentration than in mainstream smoke.
2. Existence of a large number of nonsmokers who have to inhale sidestream smoke frequently and intensively for long years at home and/or at the workplace.
3. Existence of sidestream smoke component in blood and urine of nonsmokers exposed to passive smoking, (eg, nicotine, CO-Hb in blood and Mutagens in urine.).
4. Existence of functional abnormalities in nonsmokers exposed heavily to passive smoking (eg, respiratory or circulatory function).
5. Lung tissue damage and destruction in chronic passive smokers as shown by elevated hydroxyproline excretion in urine.
6. Higher incidence of selected diseases in nonsmokers exposed heavily to passive smoking (eg, pneumonia, bronchitis, asthma, ischemic heart disease, lung and nasal sinus cancer).
7. Experimental evidence.

main effect of passive smoking on lung cancer risk results from the prolonged exposure to such promoters in sidestream smoke. The risk-inhibitory effect of a daily intake of green-yellow vegetables that are rich in β-carotene must be considered as an additional evidence for such a promoter action hypothesis of passive smoking. The hypothesis also explains why exposure to passive smoking that starts after reaching adult age can significantly influence the risk of lung cancer.

The histology of 21 cases of lung cancer in nonsmoking wives of smoking husbands was not essentially different from that in smoking women (adenocarcinoma 57.1%, squamous cell carcinoma 19.0%, and small-cell carcinoma 4.8%). A case-control study conducted within our cohort study revealed a significant dose-response relationship between adenocarcinoma of the lung and the number of cigarettes smoked daily, relative risk being 1.39 and 5.75 for smokers of 1–14 and 15 or more cigarettes daily, the chi square for the trend being 6.848 with a one-tail p value of 0.004. Therefore the predominance of adenocarcinoma of the lung in nonsmoking women with smoking husbands should not be considered unfavorable evidence for promoter action hypothesis of passive smoking. In passive smoking, sidestream smoke usually is inhaled through the nose, whereas in active smoking mainstream smoke always is inhaled through the mouth. This difference could be a reason for the elevated risk of nasal sinus cancer in passive smokers. The mechanism of the action of passive smoking on the risk of ischemic heart disease, however, must be explained in different ways (eg, a combined action of carbon monoxide and nicotine).

In summary, to reduce the effect of active and passive smoking and to encourage the effect of nutrition, in particular β-carotene intake, would be the most productive course for lung cancer prevention. For selected persons exposed to other known carcinogens, eg, those related to occupation or radiation, such environmental exposure also must be minimized in addition to the preventive measures focused on lifestyle variables given above.

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Dark Tobacco and Lung Cancer in Cuba [1, 2]

Olga G. Joly, *D.D.S., Sc.D.*, [3, 4] Jay H. Lubin, *Ph.D.*, [5] *and* Magaly Caraballoso, *M.D.* [6, 7]

ABSTRACT—A retrospective epidemiologic study of 826 cytologically and/or histologically confirmed lung cancer cases (219 females and 607 males), 979 hospital controls, and 539 neighborhood controls was undertaken in Havana, Cuba, to investigate whether the high lung cancer mortality rates in this country could be explained by the cigarette and cigar consumption habits, including the smoking of dark-tobacco cigarettes. Relative risk(s) (RR) of lung cancer among cigarette smokers were 7.3 in women and 14.1 in men and increased consistently with various measures of exposure to smoke. The findings suggested that duration of smoking, daily number of cigarettes consumed, and inhalation practices have independent effects. Most Cubans smoked dark tobacco. RR were higher for dark-tobacco users than for light-tobacco users (RR = 8.6 vs. 4.6 for women and 14.3 vs. 11.3 for men), but the differences were reduced after adjustment for amount smoked. Cigarette smoking was associated with all histologic types of lung cancer, although the risk for adenocarcinoma was lower than that for the other types. Men who smoked exclusively cigars had a fourfold risk of lung cancer. Mixed smokers (i.e., cigar and cigarette smokers) had a greater RR than cigarette-only smokers (15.0 vs. 14.1), which was perhaps related to the unusually deep and frequent inhalation of cigar smoke. The data support the hypothesis that smoking patterns account for the higher lung cancer mortality in Cuba than in other Latin American countries.—JNCI 1983; 70:1033–1039.

A report on the health conditions in the Americas in the early 1970's revealed that Cuba had the highest lung cancer mortality rates for women in the American region; age-adjusted rates per 100,000 were 8.7 in Cuba as compared to 5.8 in the United States, 3.5 in Argentina, and 2.3 in Uruguay. Corresponding rates for men were the fourth highest in the American region: they were 24.3 in Cuba as compared to 26.9 in the United States, 27.8 in Argentina, and 25.7 in Uruguay (*1*). Of possible significance is that a high proportion of cigarettes smoked in Latin America are made of a dark, locally grown tobacco that has a higher concentration of phenols and nicotine and is more alkaline than the light Virginia-grown type of tobacco (*2*). Skin painting experiments on mice suggested that refined tar from Colombian dark tobacco has about twice the carcinogenic potential as refined tar from U. S. tobacco (*3*). A study of mortality patterns in 11 Latin American cities showed that La Plata, Argentina, had the highest lung cancer male-adjusted mortality rate (59.0/100,000); the explanation offered was the known high consumption of dark tobacco among the population of this city (*4*). This paper reports results of a case-control study undertaken to evaluate the role of smoking habits in the causation of lung cancer among Cuban women and men.

METHODOLOGY

A case-control study of lung cancer was conducted in Havana, Cuba, a city of approximately 2 million inhabitants (one-fifth of the country's population). Cases were drawn from patients admitted to all the city's 12 main general hospitals with a tentative diagnosis of lung cancer; females were ascertained from 1978 to 1980 and males from 1979 to 1980. In each of the participating hospitals, a staff member was assigned to ensure prompt identification and reporting of all suspected lung cancer patients to the Central Study Office located at the Institute of Oncology and Radiobiology. Only those patients who had their final diagnosis confirmed by cytology and/or histology were included in the study. To ensure consistency of criteria, an ad hoc Pathology Review Committee performed all typing according to the World Health Organization's Classification of Lung Cancer.

A hospital control selected from patients with a current admission for a non-smoking-related disease was matched to each case by sex, age (±5 yr), hospital of admission, and admission date (±15 days). When several controls were available, the closest in admission date was chosen. Not accepted as controls were patients with diseases such as cancers of the upper digestive and respiratory tracts, pancreas, kidney, and urinary bladder; chronic bronchial disease; duodenal and gastric ulcers; and cardiovascular diseases known to be related to smoking. The main diagnostic categories among female and male hospital controls, respectively, were in percentages: digestive diseases (15.1 and 12.8), malignant and benign neoplasms (21.9 and 23.7), eye diseases (6.4 and 15.6), respiratory diseases including tuberculosis (14.5 and 9.3), traumatisms (7.3 and 15.6), diabetes and metabolic disorders (9.6 and 2.6), and skin diseases (4.1 and 7.3); in smaller proportions were the categories arthritis,

Abbreviation used: RR=relative risk(s).

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[2] Sponsored jointly by the International Agency for Research on Cancer (by subcontract to National Cancer Institute Prime Contract No. N01CP-55666) and the Ministry of Public Health, Cuba.

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asthma, anemia, renal diseases, and other miscellaneous conditions.

For each case residing in Havana, an additional neighborhood control was selected and was matched with regard to place of residence (on the same block or as close as possible), sex, and age (±5 yr) in an effort to adjust for socioeconomic and general environmental factors. Selection of the neighborhood control was achieved through the cooperation of neighborhood community affairs committees who made available listings of residents along with information on sex and date of birth. Initially, two hospital controls were matched to each non-Havana resident case, but this was reduced to one hospital control after the 2d year of the study.

As potential study subjects were identified, interviews were conducted with the use of a standardized structured questionnaire. Data were collected on demographic characteristics: educational level; lifelong smoking, residential, and occupational histories; alcohol consumption; and exposure to cooking fuels. The population proved extremely cooperative, with all persons contacted agreeing to participate in the study.

Although the neighborhood controls were interviewed at home and the cases and hospital controls were interviewed in the hospital, minimal interviewer bias was anticipated since most hospital interviews were not conducted at bedside but in adjacent private surroundings. While complete interviewer blindness would have been impossible to achieve, the interviewers were made aware that the questionnaire was administered only to gather general health and disease data from both hospitalized and nonhospitalized populations.

Data on a total of 826 confirmed lung cancer cases (219 females and 607 males), 979 hospital controls, and 539 neighborhood controls were analyzed with the use of procedures for matched (*5*) and unmatched (*6, 7*) studies. Hospital and neighborhood controls for both female and male cases were quite similar regarding sociodemographic characteristics, such as years of education, marital status, and age at interview (table 1). Furthermore, the distribution of the smoking-related variables in both control groups and the RR of lung cancer resulting from the comparison of cases with either control group with the use of matched or unmatched procedures were also similar. It was decided thenceforth to present only the unmatched analyses in which cases were compared with both types of controls combined into a single group.

Measures of exposure to cigarette smoking (i.e., duration of smoking, number of cigarettes smoked daily, and frequency and depth of inhalation) were based on lifetime information on all cigarette brands used; 9.2% of the respondents smoked one or two brands, and 7% smoked a total of three brands. Identification of dark- versus light-tobacco smokers was made from reported brands. Measures of exposure to tar were based on information from only the four most popular cigarette brands currently smoked, which were analyzed by the Oak Ridge National Laboratory, Oak Ridge, Tenn., for yields of tar, nicotine, CO, and CO_2. Therefore, a substantially smaller number of subjects were available for the investigation of smoke content since only persons consuming exclusively the four brands tested could be used.

TABLE 1.—*Percentage distribution of demographic variables in cases (C), hospital (H) controls, and neighborhood (N) controls*

Variables	Females,[a] %			Males,[b] %		
	C	Controls		C	Controls	
		H	N		H	N
Age at interview, yr						
<40	4.2	6.8	4.6	4.0	2.9	2.6
40–59	40.6	42.4	38.6	29.2	28.6	26.4
≥60	55.2	53.4	56.8	66.8	69.0	71.1
Mean age	59.9	59.7	60.9	63.3	63.6	64.5
Education, yr						
<7	83.1	81.7	83.8	80.5	76.0	76.7
7–9	11.9	13.0	10.8	12.5	13.2	15.9
≥10	5.0	5.3	5.4	7.0	10.7	7.4
Mean yr	4.5	5.0	5.2	5.2	5.6	5.8
Marital status						
Single	4.1	7.3	6.1	9.9	12.1	8.9
Married	61.6	57.3	58.5	74.9	71.1	76.2
Divorced	15.1	13.4	11.5	7.1	7.5	5.9
Widowed	19.2	22.1	24.3	8.1	9.2	9.0

[a] The following are the total No. of females in each group: C=219, H=262, and N=148.

[b] The following are the total No. of males in each group: C=607, H=717, and N=391.

RESULTS

The ages of the lung cancer patients ranged from 23 to 8[illegible] years, with approximately one-half of the females and two-thirds of the males 60 years old or over at the time of diagnosis. Education level was similar in all groups, but slightly lower mean years of schooling were found among the cases. Approximately 60% of the women and 75% of the men were married (table 1).

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Smoking

In this study 167 of the 219 female cases (76.3%) and 595 of the 607 male cases (98.0%) ever smoked regularly, as compared to 31.0 and 80.3% of female and male controls, respectively. The corresponding proportions for female hospital and neighborhood controls were 30.5 and 31.8%, whereas for males they were 80.5 and 80.1%. A total of 12.2 and 8.1% of female and 38.9 and 39.9% of male hospital and neighborhood controls, respectively, smoked cigarettes for 50 years or more. Among case smokers, 1 female and 43 males smoked cigars only. In the following analyses cigar-only and pipe-only smokers were excluded.

TABLE 2.—*RR of lung cancer in cigarette smokers according to kind of tobacco*

Cigarette smoking	Females			Males		
	No. of cases	No. of controls	RR	No. of cases	No. of controls	RR
Nonsmokers	52	283	1.0	12	218	1.0
Cigarette smokers	166[a]	123[a]	7.3	552	709	14.1
Dark tobacco	133	84	8.6	529	674	14.3
Light tobacco	16	19	4.6	10	16	11.3
Both dark and light tobaccos	16	17	5.1	13	19	12.4

[a] Includes some unknown tobacco kind smoked.

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

The overall RR of lung cancer in cigarette smokers were 7.3 and 14.1 for females and males, respectively. Most respondents who smoked consumed the local dark-tobacco cigarettes exclusively, as reported by 80 and 96% of female and male cases, respectively, and by 68 and 95% of their corresponding controls. There were increased risks of lung cancer in both sexes associated with smoking both light and dark tobaccos, but the excess was greater for dark tobacco (RR=8.6 for dark tobacco vs. 4.6 for light tobacco among females; RR=14.3 for dark tobacco vs. 11.3 for light tobacco among males) (table 2).

With either kind of tobacco, the longer the duration of smoking or the greater the total number of cigarettes consumed the higher the risk, all trends being highly significant ($P<0.001$) (table 3). When gradients of increasing risk for duration of smoking and for number of cigarettes smoked daily were estimated with the use of a logistic model that included linear and quadratic effects, the differences in trend between dark- and light-tobacco users were not statistically significant.

Analysis of all cigarette smokers regardless of the kind of tobacco they favored indicated that cases of both sexes not only had a much higher proportion of smokers than controls, but also smoked for many more years, consumed more cigarettes daily, and were exposed to higher amounts of tar (table 4). Highly significant ($P<0.001$) linear trends in RR for these three measures of cigarette smoke exposure were noticed in both sexes; increases of 6.2-fold, 2.9-fold, and 4.5-fold for duration of smoking, daily cigarette consumption, and lifetime tar exposure, respectively, were found between the lowest and the highest levels of exposure in females; the corresponding increases in males were 4.3-fold, 4.0-fold, and 1.6-fold.

When RR for duration of smoking, daily cigarette consumption, and lifelong tar exposure were each computed with separate adjustment for the other two, there remained a consistent pattern of increasing risk with duration of smoking and mean number of daily cigarettes (table 5). The increasing risk with duration of smoking was greater for females (over fourfold) than for males (twofold), although the increases with the daily number of cigarettes were greater for males. While RR increased with tar intake, the risk patterns were less convincing than for duration of smoking and amount smoked. These results suggest that duration of smoking and number of cigarettes acted independently, whereas risk with tar intake was less clear, due perhaps to the high correlation of tar with duration of smoking. Because of the small number of brands tested and the high correlation between the smoke components, the effects of tar could not be isolated from other constituents of tobacco smoke, such as nicotine, CO, or CO_2.

The earlier in life cases began to smoke, and the more frequently and the more deeply they inhaled, the higher were their risks of developing lung cancer, even after control for duration of cigarette use; linear trends were significant and did not differ much between females and males (table 6). Cases of both sexes who reported cessation of smoking 1–4 years prior to interview had an increased risk of lung cancer that declined after the 5th year of smoking cessation.

TABLE 3.—*RR of lung cancer in nonsmokers and in dark-, light-, and mixed-tobacco[a] cigarette smokers by duration of smoking and number of cigarettes smoked daily[b]*

Variable	Females			Males		
	No. of cases	No. of controls	RR	No. of cases	No. of controls	RR
Nonsmokers	52	283	1.0	12	218	1.0
Duration of dark-tobacco smoking, yr[c]						
1–19	6	15	2.2	9	43	3.8
20–39	33	31	5.8	107	206	9.4
≥40	94	38	13.5	413	425	17.7
Duration of light-tobacco smoking, yr[d]						
1–19	5	10	2.7	1	4	4.5
≥20	11	9	6.7	9	12	13.6
Duration of mixed-tobacco smoking, yr						
1–39	12	15	4.4	10	12	15.1
≥40	4	3	7.3	3	7	7.8
No. daily, dark-tobacco[c]						
1–9	26	23	6.2	16	50	5.8
10–19	64	35	10.0	210	304	12.6
20–99	10	15	6.6	116	165	12.8
≥50	24	11	11.9	187	155	21.9
No. daily, light-tobacco[d]						
1–19	9	15	3.3	2	8	4.5
≥20	7	4	9.5	8	8	18.2
No. daily, mixed-tobacco						
1–19	6	13	2.5	5	10	9.1
≥20	10	5	10.9	8	9	16.2

[a] Mixed tobacco=both dark and light tobaccos.
[b] All tests for linear trend relative to those for nonsmokers. $P<0.001$.
[c] Dark-tobacco smokers exclusively.
[d] Light-tobacco smokers exclusively.

TABLE 4.—*RR of lung cancer by several measures of cigarette smoke exposure*

Measures	Females			Males		
	No. of cases	No. of controls	RR[a]	No. of cases	No. of controls	RR[a]
No. of years of smoking						
<20	13	28	2.5	11	48	4.2
20–29	18	26	3.8	38	61	11.3
30–39	31	24	7.0	85	165	9.4
40–49	47	24	10.7	168	182	16.8
≥50	57	20	15.5	250	253	18.0
Mean No. of cigarettes/day						
1–9	33	38	4.7	16	54	5.4
10–19	72	49	8.0	217	318	12.4
20–29	28	22	6.9	126	175	13.1
≥30	32	13	13.4	193	161	21.8
Lifetime tar exposure[b]						
I	17	28	3.3	56	79	12.9
II	33	12	15.0	59	65	16.5
III				62	56	20.1

[a] All RR relative to those of nonsmokers; all tests of linear trend, $P<0.001$.
[b] Levels of tar in milligrams for females were: I=<11,000 and II=≥11,000. For males they were: I=<15,640, II=15,640–24,079, and III=≥24,080.

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TABLE 5.—*RR of lung cancer by several measures of cigarette exposure controlling for each other*

Control for:	RR for No. of years smoked					
	Females			Males		
	1–29	30–39	≥40	1–29	30–39	≥40
No. of daily cigarettes	1.0	2.0	4.4[a]	1.0	1.1	2.1[a]
Tar	1.0	6.7	5.8[b]	1.0	1.5	1.7[c]

Control for:	RR for No. of daily cigarettes							
	Females				Males			
	1–9	10–19	20–29	≥30	1–9	10–19	20–29	≥30
No. of years	1.0	1.2	1.2	2.3[c]	1.0	2.1	2.3	3.6[a]
Tar	1.0	1.3	0.6	—	1.0	0.8	1.9	1.3

Control for:	RR for lifetime tar exposure, mg				
	Females		Males		
	<11,000	≥11,000	<15,640	15,640–24,079	≥24,080
No. of years	1.0	1.6	1.0	1.1	1.2
No. of daily exposures	1.0	4.1[b]	1.0	1.3	1.2

[a] Test for linear trend, $P<0.001$.
[b] Test for linear trend, $P<0.01$.
[c] Test for linear trend, $P<0.05$.

This initial elevated risk may reflect cases who stopped smoking because of respiratory disorders antecedent to clinical lung cancer.

No significant differences were noted between cases and controls of either sex with respect to cigarette butt length or use of filtered cigarettes; most smokers consumed at least three-fourths of the cigarette, and less than 5% of smokers used filtered cigarettes. Cubans usually purchased cigarettes with filters only when the ones without filters were not available; a common practice among the Cubans was to remove the filter before lighting.

TABLE 6.—*RR of lung cancer by age smoking started, frequency and depth of inhalation of smoke, and years since last smoked, adjusted for duration of cigarette use*

Cigarette smoking	Females			Males		
	No. of cases	No. of controls	RR	No. of cases	No. of controls	RR
Age started, yr						
≥25	23	41	1.0[a]	18	70	1.0[b]
15–24	67	47	1.7	217	357	2.1
<15	76	35	2.4	317	282	3.4
Frequency of inhalation						
Rarely or never	24	40	1.0[b]	56	150	1.0[b]
Sometimes	16	17	1.4	52	55	2.6
Always	125	65	2.9	442	501	2.4
Depth of inhalation						
Never	19	35	1.0[b]	43	110	1.0[b]
Slightly	26	31	1.5	77	109	1.9
Medium	31	14	3.5	65	110	1.5
Deeply	90	43	3.2	362	378	2.4
Years since last smoked						
Current smokers	132	96	1.0	451	524	1.0[c]
1–4	19	8	2.0	38	36	1.2
≥5	15	19	0.9	63	149	0.6

[a] Test for linear trend adjusted for duration of cigarette use, $P<0.05$.
[b] Test for linear trend adjusted for duration of cigarette use, $P<0.001$.
[c] Test for linear trend adjusted for duration of cigarette use, $P<0.01$.

Histologic Type of Lung Cancer

The four main histologic types of lung cancer were almost equally represented among females; in males the squamous type was predominant (36%), followed by the poorly differentiated type (27%), and the undifferentiated type (23%), whereas adenocarcinoma was by far the less frequent (14%).

The risk of lung cancer increased significantly with longer duration of cigarette smoking for all histologic types ($P<0.001$); the greatest risks were associated with the squamous type in females and the undifferentiated type in males (table 7). In spite of the distributional differences in duration of cigarette use and in histology, the risks in smokers of 30 years or more relative to those in nonsmokers were not much different between the sexes. The RR for 1–29 years of exposure were larger in males for all but the adenocarcinoma type. Thus females had a steeper gradient of RR with years of cigarette consumption than did males for the squamous, undifferentiated, and poorly differentiated types, whereas for adenocarcinoma the gradients with duration were similar in both sexes.

Although squamous, undifferentiated, and poorly differentiated types of lung cancer did not differ significantly among themselves insofar as duration of smoking, females with all these three types were exposed significantly longer to cigarette smoke than those with adenocarcinomas (table 8). Adenocarcinoma was the most common histologic type among nonsmokers (48 and 42% in females and males, respectively) whereas it was infrequently seen among smok-

TABLE 7.—*RR of lung cancer according to duration of smoking and histologic type of lung cancer*[a]

Duration of smoking, yr	Histologic type			
	Squamous[b]	Undifferentiated[c]	Poorly differentiated[d]	Adenocarcinoma[e]
	Females			
1–29	4.4	3.9	3.2	2.1
30–39	9.4	15.6	7.8	2.7
40–49	31.4	20.6	5.4	4.7
≥50	51.9	28.3	13.1	4.0
	Males			
1–29	15.6	26.0	6.4	2.0
30–39	15.9	26.4	7.7	3.2
40–49	39.5	40.7	10.8	5.3
≥50	42.2	50.0	10.2	5.7

[a] Risks relative to those in nonsmokers; all trends were significant, $P<0.001$.
[b] There were 54 females and 219 males with the squamous type.
[c] There were 58 females and 138 males with the undifferentiated type. Inasmuch as there were no nonsmoking cases among the 138 males, one case was added in calculation of RR.
[d] There were 48 females and 165 males with the poorly differentiated type.
[e] There were 58 females and 82 males with adenocarcinoma.

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BLE 8.—*Percentage distribution of histologic types of lung cancer by duration of cigarette smoking and sex*[a]

Histologic type[b]	Duration of smoking, yr					Total No. of each histologic type
	0	1–29	30–39	40–49	≥50	
Females						
Squamous	11.1	9.3	9.3	29.6	40.7	54
Undifferentiated	14.0	14.0	19.3	24.6	28.0	57
Poorly differentiated	27.1	16.7	18.8	12.5	25.0	48
Adenocarcinoma	43.1	17.2	10.3	17.2	12.1	58
Males						
Squamous	1.0	7.3	11.7	32.2	47.8	205
Undifferentiated	0.0	10.4	16.0	27.2	46.4	125
Poorly differentiated	3.2	10.4	18.8	29.2	38.3	154
Adenocarcinoma	6.5	6.5	15.6	28.6	42.9	77

[a] Excludes 1 female and 3 males with tumors of mixed histology.
[b] Test of independence among types 1–3—females: χ^2_6=13.3, P=0.10; males: χ^2_6=12.5, P=0.13. Test of independence among types 1–3 and 4—females: χ^2_4=20.1, P=0.001; males: χ^2_4=8.6, P=0.07.

n of 50 years or more (12 and 13% in females and males, pectively).

gar Smoking in Males

A separate analysis was done on the 216 male cases and 9 controls who smoked either cigars only or cigars plus garettes (mixed smokers). (The 5 females, 1 case and 4 trols, who smoked cigars were excluded from analysis.) he risks of lung cancer in both groups of smokers were nificantly greater than those in nonsmokers; those males o smoked only cigars had an overall risk of 4.4 and those

BLE 9.—*RR of lung cancer in male nonsmokers, in male smokers cigars only, and in male smokers of both cigars and cigarettes by duration of smoking and daily consumption*

Variables	No. of cases	No. of controls	RR
Nonsmokers			
	12	218	1.0
Cigar-only smokers			
uration of smoking, yr			
1–39	8	49	3.0
40–49	9	54	3.0
≥50	26	76	6.2[a]
ily consumption			
1–2	8	35	4.2
3–4	13	75	3.2
≥5	[illegible]	[illegible]	[illegible]
Mixed smokers[b]			
ration of smoking, yr			
1–39	78	112	12.7
40–49	42	47	16.2
≥50	53	51	18.9[a]
ily consumption			
1–2	71	88	14.7
3–4	56	71	14.3
≥5	46	51	16.4

[a] Test for linear trend relative to 1–39 yr, P<0.05.
[b] Mixed smokers = smokers of both cigars and cigarettes.

TABLE 10.—*RR of lung cancer in male smokers of cigars only by age smoking started, years since last smoked, and frequency and depth of inhalation adjusted for duration of cigar use*

Variables	No. of cases	No. of controls	RR
Total	43	179	4.4
Age started, yr			
≥25	7	34	1.0
15–24	17	91	0.8
<15	19	54	1.2
Frequency of inhalation			
Rarely or never	21	126	1.0[a]
Partially	8	20	2.3
Always	14	33	2.5
Depth of inhalation			
Never	17	105	1.0[b]
Slightly	9	42	1.3
Moderately	5	17	1.8
Deeply	12	15	4.9
Years since last smoked			
Current smokers	36	141	1.0
1–4	2	13	0.7
≥5	5	25	1.1

[a] Test for linear trend, P<0.01.
[b] Test for linear trend, P<0.001.

males who were mixed smokers had an overall risk of 15.0. Risks increased significantly with duration of cigar smoking in those who smoked only cigars as well as in those who were mixed smokers, but the increases with the number of cigars smoked daily in either group of smokers were not significant (table 9).

Male cases who smoked cigars exclusively began their habit earlier in life than the controls; however, after control for duration it was found that age at which smoking was started or years since cessation of smoking did not influence the risk of lung cancer, although the power to detect effects independent of duration was small. In contrast, the RR did increase significantly with frequency and depth of smoke inhalation even after adjustment for duration of smoking (table 10).

DISCUSSION

The similarity in smoking prevalence and smoking characteristics between both groups of controls was likely due to the high prevalence of smoking in Cuba and the acceptance of hospital controls whose current admission was for a non-tobacco-related disease. In fact, in a 1979 population-based survey in Havana, the frequency of smoking was found to be 33.0% in women and 78.0% in men over 30 years of age (Marcias Castro I: Personal communication). These smoking prevalences are considerably higher than those reported in the early 1970's for eight other Latin American cities, where the overall frequencies of smoking were 18.5 and 47.8%, respectively, in the age group of 25–74 years, ranging from 6.1% (Lima, Peru) to 28.1% (Santiago, Chile) for females and from 35.4% (Lima) to 55.4% (La Plata) for males (*2*). Furthermore, not only a greater proportion of Cubans than other Latin Americans smoked, but also those who did smoke consumed almost twice as many daily cigarettes, started smoking earlier in life, smoked for more years, and preferred the dark type of tobacco and nonfilter ciga-

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rettes. These differences in smoking patterns and the high risk of lung cancer related to cigarette smoking found in our study indicate that smoking habits may account for the higher lung cancer rate in Cuba than in other areas of Latin America.

On the basis of calculations of attributable risk, we estimate that a maximum of 66% of female and 91% of male lung cancer cases in Cuba are due to smoking. Analyses of other variables, such as place of birth, residence, alcohol consumption, and environmental exposure measured by lifelong presence and type of nearby factories, occupation, and use of cooking fuels, did not discriminate between cases and controls. A separate analysis by residence (Havana vs. not Havana) failed to show a differential risk between lifetime rural or urban residency.

It has been suggested (*3, 4*) that smoking the dark type of tobacco product is more deleterious than smoking the light variety. We did find a higher level of risk linked to smoking dark-tobacco cigarettes, but the excess was reduced after accounting for duration and number of cigarettes smoked daily. However, the power to detect a difference between the tobacco types was small due to the very low proportion of light-tobacco cigarette smokers. It has been assumed that, because of their alkalinity, dark-tobacco cigarettes could not be inhaled as deeply and as frequently as light-tobacco ones, but we found that the tobacco type had no influence on the inhalation practices. We believe that the differential risks by type of tobacco require further exploration, preferably in communities where the discrepancy between proportions of light- and dark-tobacco users is not as extreme as in Cuba.

The RR of lung cancer associated with smoking were lower in women than in men, partly related to lower cigarette consumption by women. The RR tended to be slightly lower in women for all smoking categories, such as number of years smoked, mean number of daily cigarettes consumed, lifetime tar exposure, and age starting to smoke, in agreement with prior reports (*8–11*). However, the sex differential risk disappears in frequently and deeply inhaling females for whom the risk is even slightly higher than that in males. This same finding was noted for squamous cell cancers, the histologic type with the strongest relation to smoking. Hence it appears that no biologic protection is afforded to smoking women, and the lower RR result from somewhat lower average smoke exposure within each of the broad categories of age smoking started, duration of smoking, and daily cigarette consumption.

Although differences in the histologic classification criteria complicate the comparison with data from other studies, most studies have reported a preponderance of adenocarcinoma (*12–16*), squamous type (*17*), undifferentiated type (*18*), or similar proportions of undifferentiated type and adenocarcinoma (*19, 20*) in females. In our study, no histologic type was predominant among females. Among males, however, there was agreement in that the squamous type of cancer appeared to predominate (*15, 21, 22*). Similar to the results in other reports, the gradient in RR was steepest for squamous cell carcinomas, but increased risks were found for all types of lung cancer including adenocarcinoma.

Because male cigarette smokers had a threefold higher risk of lung cancer than cigar-only smokers (14.1 vs. 4.4), it was expected that mixed smokers (i.e., smokers of cigarettes plus cigars) would experience a risk intermediate between the risks of the first 2 groups. However, we found instead that cases who were mixed smokers had a slightly greater risk than those smoking cigarettes only (15.0 vs. 14.1); to account for this unexpected finding, we examined the inhalation practices among cases and controls. Results indicated that 31.7 and 41.5% of all cases who smoked cigars only were frequent and deep inhalers of *cigar* smoke, whereas among those who were mixed smokers the percentages were higher, 54.0 and 60.2%, respectively (table 11). Even greater differences in inhalation practices were observed between both groups of smokers in the controls. Conversely, the inhalation practices of *cigarette* smoke did not differ significantly between smokers of cigarettes exclusively and mixed smokers, except for inhalation frequency among the controls. It thus appears that the manner in which mixed smokers inhaled their cigarette smoke determined the manner in which they also inhaled their cigar smoke, which in turn may explain the high risk among the mixed smokers.

TABLE 11.—*Percentage distribution of inhalation practices in male users of cigars only or cigarettes only and in male smokers of both cigars and cigarettes*

Inhalation	Percent inhaling[a]			
	Cigar smoke		Cigarette smoke	
	Cigar only	Mixed[b]	Cigarette only	Mixed[b]
Cases				
Frequency				
Never or rarely	48.8	27.3	8.8	11.8
Part of the time	19.5	18.6	8.0	13.7
Always or most of the time	31.7	54.0	83.1	74.5
	P=0.02		P=NS	
Depth				
Never	39.0	16.8	6.5	9.4
Slightly	19.5	23.0	13.4	15.1
Deep or moderate	41.5	60.2	80.1	75.5
	P=0.009		P=NS	
Controls				
Frequency				
Never or rarely	69.6	41.2	18.8	26.9
Part of the time	11.7	14.6	6.9	9.9
Always or most of the time	18.7	44.2	74.3	63.2
	P<0.001		P=0.01	
Depth				
Never	57.9	28.9	14.1	19.0
Slightly	23.4	23.9	14.1	18.5
Deep or moderate	18.7	47.2	71.7	62.6
	P<0.001		P=NS	

[a] NS=not significant.
[b] Both cigars and cigarettes.

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Volume 5, Number 3, 1983

ENVIRONMENTAL MUTAGENESIS

Official Journal of the Environmental Mutagen Society

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shown to be mutagenic in Salmonella. In this test, CSC seems to possess frameshift mutagens that require metabolic activation, and the majority of the mutagenic activity resides in the basic fraction. A small amount of activity is in the acidic fraction, and very little is in the neutral fraction. Recent work indicates that the BP content accounts for little of the mutagenic activity of CSC. However, pyrolysis products of amino acids may account for nearly 50% of the mutagenic activity of CSC as detected in Salmonella. Additional work indicates that the specific mutagenic activity of CSC is similar for low or high tar cigarettes, and that filters do not remove much mutagenic activity. The specific mutagenic activity of tobacco products is: cigar > cigarette > pipe. CSC and the urine of smokers have been shown to induce SCEs in the absence of metabolic activation, and some studies have shown that smokers have a greater frequency of SCEs than do nonsmokers. The gas phase of cigarette smoke has been shown to induce SCEs in human lymphocytes, which contain metabolic activation enzymes. The gas phase of cigarette smoke has induced reciprocal mitotic recombination and petites in yeast; and CSC and cigarette smoke have induced mitotic gene conversion and reverse mutation in yeast. Cigarette smoke also has been shown to induce reciprocal mitotic recombination in yeast. CSC is also mutagenic in the fungus, N. crassa, in the presence or absence of S9, and potent direct-acting mutagenic activity was found in a PAH-containing fraction and a basic fraction; however, an acidic fraction was not mutagenic. CSC and cigarette smoke have induced sex-linked recessive lethals in Drosophila, and CSC is mutagenic in mammalian cells. There are a few reports of sperm abnormalities in smokers, and smoking mothers experience increased numbers of spontaneous abortions, and their live-born children have a reduced birthweight. There is also the possibility that children of smoking mothers incur an increased risk of congenital defects; however, this point requires further study. CSC and cigarette smoke have been shown to induce cell transformation, and CSC has transformed fetal cells that were exposed in utero. CSC and cigarette smoke have induced cancer in laboratory animals. In conclusion, cigarette smoke has been shown to induce somatic cell mutations that may lead to cancer, and it may induce germ cell mutations that could cause heritable defects.

Ca-2

CIGARETTE SMOKING AND MORTALITY RATES: EPIDEMIOLOGICAL AND PATHOLOGICAL EVIDENCE. L. Garfinkel, American Cancer Society, 4 West 35th Street, New York, NY 10001.

Evidence is presented on the relationship between cigarette smoking and death rates from the American Cancer Society's (ACS) prospective study, 1959-1972. Mortality rates for total deaths increase with the number of cigarettes smoked per day, compared to nonsmokers. Similar increases are shown for coronary heart disease and a number of other diseases including lung cancer. The rate of lung cancer increases steeply with the amount of cigarette smoking until it is 18 times as great for those who smoked 40+ cigarettes a day compared to those who never smoked. Supplementary evidence of the effects of cigarette smoking have been obtained from autopsy studies. Cellular changes preceding invasive cancer are seen in direct proportion to the number of cigarettes smoked per day before death. Epidemiologic and pathologic evidence demonstrate that ex-cigarette smokers have lower mortality rates than those who continue to smoke. Mortality rates in relation to tar and nicotine content of cigarettes were also investigated. Smokers of low tar/nicotine (T/N) brands had death rates for total deaths averaging 16% lower than high T/N smokers. The lung cancer death rate of low T/N smokers was about 26% less than high T/N smokers. These findings were confirmed in a study of changes in the tracheobronchial

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tree. Data from the ACS study showed that low T/N smokers are able to quit smoking at a higher rate than high T/N smokers. Trends in younger male smokers indicate there may be a drop in the lung cancer rate in the next 10 years. Female lung cancer rates, however, will continue to rise.

Ca-3

TOBACCO USE: BEHAVIORAL, PHYSIOLOGICAL AND PHARMACOLOGICAL DETERMINANTS. J. Grabowski, Behavioral Pharmacology Branch, Clinical Research Division, NIDA, 5600 Fishers Lane, Rockville, MD 20857.

This presentation (i) reviewed historical aspects of tobacco use, (ii) delineated the role of behavioral pharmacology and the self-administration model for scientific analysis of tobacco use behavior, (iii) considered the utility of the unifying descriptive concepts of "drug-behavior-environment interactions" and "commonalities of dependence disorders," and (iv) examined clinical and naturalistic aspects of the development, maintenance and elimination (and hence treatment) of tobacco use. Historically, tobacco use in its various forms has been characterized as both beneficial in the treatment of diverse ills and as causally related, or at least correlated, with equally numerous health risks. In addition, social, moral and economic issues have surrounded tobacco use for centuries. Only recently has a scientific analysis of behavior permitted an increasingly thorough, although by no means exhaustive, understanding of the mechanisms that appear to contribute to acquisition, maintenance and elimination of tobacco use. Behavioral pharmacology has provided a conceptual framework, strategy and technology for the analysis of drug self-administration in the

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Aus dem Hygiene-Institut der Universität Wien
(Vorstand: Univ.-Prof. Dr. med. *Heinz Hamm*)
Abteilung Sozialmedizin (Leiter: Univ.-Prof. Dr. med. *Michael Kunze*)

Lungenkrebsrisiko bei Angehörigen der Berufsgruppe „Steinabbau und -verarbeitung"

Lung Cancer Risk in Workers Belonging to Occupation "Mining and Processing of Stone"

CHRISTIAN VUTUC

Abstract

Out of 1580 male lung cancer patients and 3160 controls (data collected in a nation wide study) 177 patients and 197 controls belonged to the occupation "mining and processing of stone" (asbestos, metalls and coal excluded). 164 (92.6%) patients had a Kreyberg I tumor, 13 patients a Kreyberg II tumor. There are significant more smokers among patients (98.9%[a]), all patients with a K I tumor were smokers, compared to the controls (82.2%). Patients had a significant longer smoking career (40.9 years[a]) and a higher tar exposure (TE = 2544)[b] compared to the controls (36.2 years, TE = 2223). Lung cancer risk (adj. for age, years of occupation, TE) of smokers belonging to occupation "stone" compared to smokers belonging to group "white collar" (no occupational exposure in their anamnesis) was R = 2.0[a]. Significantly higher risks (adj. for age, TE) were in relation to years of occupation: < 10 years: R = 2.2[a], 11–20 years: R = 2.7[a], 21–30 years: R = 2.6[a].

[a] $P < 1\%$; [b] $P < 5\%$.

Zusammenfassung

Unter 177 Lungenkrebspatienten der Berufsgruppe „Steinabbau und -verarbeitung" (= „Stein") waren signifikant mehr Zigarettenraucher (98,9%[a]) als unter 197 Kontrollpersonen (82,2%). Signifikante Unterschiede zwischen Patienten und Kontrollen bestehen bei: Jahre geraucht: 40,9[a] (36,2); Teerexpositionswert (TEW): 2544[b] (2223). Raucher der Gruppe „Stein" weisen nach Adjustierung von Alter, Berufsdauer und TEW gegenüber Rauchern der Gruppe „white collar" ein signifikant höheres Lungenkrebsrisiko (R = 2,0[a]) auf. Signifikante Werte bestehen für eine Berufsdauer von weniger als 10 Jahren (R = 2,2[a]), 11–20 Jahren (R = 2,7[a]) und 21–30 Jahren (R = 2,6[a]).

[a] $P < 1\%$; [b] $P < 5\%$.

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Einleitung

Im Rahmen einer Analyse des berufsbedingten Risikos bei männlichen Lungenkrebspatienten aus Daten einer Fall-Kontroll-Studie wurde bereits über die Berufsgruppen „Metallgewinnung und -verarbeitung" (6), „Chauffeure" (7) sowie „Gummi-Farbstoffe-Chemikalienerzeugung und -verarbeitung" (8) berichtet. Die vorliegende Arbeit analysiert die Rauchgewohnheiten sowie das berufsbedingte Lungenkrebsrisiko von Angehörigen der Berufsgruppe „Steinabbau und -verarbeitung". Wie in den vorangegangenen Analysen konnte das berufsbedingte Risiko nur für Zigarettenraucher bestimmt werden, da wegen der kleinen Fallzahl von Niemalsrauchern unter den Bronchuskarzinompatienten des Untersuchungs- und Vergleichskollektivs eine diesbezügliche Auswertung nicht möglich war.

Patientengut und Methodik

Über die Durchführung und Methodik der im gesamten Bundesgebiet durchgeführten Fall-Kontroll-Studie (Erhebungszeitraum 1976 bis 1980) wurde an anderer Stelle ausführlich berichtet (3, 5, 6); es werden in der Folge nur die wesentlichen Punkte angeführt.

Aus dem Gesamtkollektiv (1580 Patienten, 3160 Kontrollpersonen) wurden alle Personen der Berufsgruppe „Steinabbau und -verarbeitung" (= „Stein") ermittelt und deren Angaben ausgewertet. In der Berufsgruppe „Stein" nicht enthalten sind die Bereiche „Asbest, Erze, Kohle". Von den Zigarettenrauchern wurden alle jemals konsumierten Zigarettenmarken, einschließlich jeweiliger Menge und Konsumdauer, erhoben. Die Zigarettensorten wurden je nach Teergehalt einer von drei Markengruppen (3) zugeordnet (Gruppe I: < 15 mg; Gruppe II: 15–24 mg; Gruppe III: > 24 mg). Es wurde der Teerexpositionswert (= TEW) berechnet, in dem die Summen der Produkte aus täglicher Menge mal Konsumdauer/Jahre mal Gruppenfaktor (= 1, 2, 3) aller angegebenen Sorten gebildet wurde (5).

Als Vergleichskollektiv für die Berechnung des berufsbedingten Lungenkrebsrisikos wurden aus dem Gesamtkollektiv alle Personen ermittelt, bei denen aufgrund der Berufsanamnese eine berufliche Exposition (Inhalationsnoxen) ausgeschlossen werden konnte (= „white collar"). Von den 784 Zigarettenrauchern (248 Patienten, 536 Kontrollpersonen) der 1091 (252 Patienten, 839 Kontrollpersonen), die der Gruppe „white collar" zugehörten, wurden analoge Daten ausgewertet (genaue Angaben in 6).

Das Lungenkrebsrisiko (1), adjustiert für Alter (< 55, 56–65, > 66 Jahre) und TEW (< 1000, 1001–2000, 2001–3000, 3001–4000, > 4001) sowie die 95% Vertrauensbereiche (2), wurden für Raucher der Gruppe „Stein" gegenüber Raucher der Gruppe „white collar" für unterschiedliche Dauer der Berufstätigkeit berechnet.

Ergebnisse

Von den insgesamt 1580 befragten männlichen Patienten und 3160 Kontrollpersonen wurden 177 Patienten und 197 Kontrollpersonen der Berufsgruppe „Stein" zugeordnet. Von den 177 Patienten hatten 164 (92,6%) einen Tumor der Gruppe Kreyberg I, 13 Patienten (7,3%) einen Tumor der Gruppe Kreyberg II.

Von den 177 Patienten waren 175 (98,9%) Zigarettenraucher; von den 197 Kontrollpersonen haben 162 (82,2%) geraucht (jeweils einschließlich Exraucher) – signifikant weniger (X^2 27,11; $P < 1\%$). Alle Patienten mit einem K I-Tumor haben geraucht, zwei Patienten mit einem K II-Tumor waren Niemalsraucher.

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Die zwei Patienten, die niemals geraucht haben, waren zum Zeitpunkt der Diagnose 48 und 39 Jahre alt sowie 20 bzw. 5 Jahre in der Berufsgruppe „Stein" tätig. Die 35 Niemalsraucher unter den Kontrollpersonen waren durchschnittlich 65,4 Jahre alt (SF = 1,38) sowie 29,4 Jahre (SF = 1,60) berufstätig.

In Tab. 1 sind die Durchschnittswerte für Alter, Dauer der Berufstätigkeit, Jahre gerauchT und TEW der Zigarettenraucher unter den Patienten und Kontrollpersonen wiedergegeben.

Tabelle 1. Männliche Bronchuskarzinompatienten und Kontrollpersonen, Berufsgruppe „Steinabbau und -verarbeitung", Durchschnittswerte für Alter, Berufsdauer, Rauchdauer und Teerexpositionswert (1 SF)

Table 1. Male lung cancer patients and controls belonging to occupation "mining and processing of stone", mean values for age, years of occupation, years smoked and tar exposure (1 SE)

	Patienten (n = 175)		Kontrollen (n = 162)	
Alter zum Diagnosezeitpunkt	62,2	(0,78)	62,9	(0,77)
Jahre berufstätig	27,7	(0,83)	29,4	(0,80)
Jahre geraucht	40,9[a]	(0,81)	36,2	(0,96)
Teerexpositionswert	2544[b]	(103)	2223	(114)

[a] $P < 1\%$; [b] $P < 5\%$.

Tabelle 2. Lungenkrebsrisiko (adjustiert nach Alter und Teerexpositionswert) von Zigarettenrauchern der Berufsgruppe „Steinabbau und -verarbeitung" (S) gegenüber Zigarettenrauchern der Gruppe „white collar" (WC) nach Dauer der Berufstätigkeit („white collar" R = 1,0)

Table 2. Lung cancer risk (adjusted for age and tar exposure) of smokers belonging to occupation "mining and processing of stone" (S) compared to smokers belonging to group "white collar" (WC) for different years of occupation ("white collar" R = 1.0)

	Jahre berufstätig								insges.	
	–10		11–20		21–30		31–40		40 +			
	S	WC	S	WC	S	WC	S	WC	S	WC	S	WC
Patienten	18	10	31	24	58	76	51	96	17	42	175	248
Kontrollen	9	26	29	68	54	159	67	214	12	69	162	536
RR	2,2		2,7		2,6		1,6		1,8		2,0	
95% Vertr.-bereich	1,6–3,0		1,5–4,7		1,6–4,4		1,0–2,6		0,8–4,4		1,6–2,7	
χ^2	20,07[a]		10,19[a]		13,42[a]		3,02		1,37		27,54[a]	

[a] $P < 1\%$.

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Patienten haben sig. länger geraucht (t = 3,70; P < 1%) und weisen einen sig. höheren TEW (t = 2,09; P < 5%) auf als Kontrollpersonen.

Kontrollpersonen waren sig. häufiger (X^2 7,23; P < 1%) Exraucher (n = 35, 46,3%) sowie sig. länger (t = 3,59; P < 1%) abstinent (15,2 Jahre, SF = 1,29) als Patienten (n = 55, 31,4%; 8,58 Jahre, SF = 1,18).

In Tab. 2 ist das adjustierte (Alter, TEW) Lungenkrebsrisiko von Rauchern der Gruppe „Stein" gegenüber Rauchern der Gruppe „white collar" nach Berufsdauer dargestellt. Bis zu einer Berufstätigkeit von 30 Jahren weisen Angehörige der Gruppe „Stein" ein sig. höheres (P < 1%) Lungenkrebstisiko auf.

Diskussion

Die dominierende Bedeutung des Zigarettenkonsums für das Entstehen von Lungenkrebs im Untersuchungskollektiv „Stein" geht deutlich aus dem extremen Rauchverhalten der Patienten hervor (gegenüber den Kontrollpersonen sig. Unterschiede bei Rauchdauer und TEW). Mit Ausnahme von zwei Personen haben alle Patienten regelmäßig Zigaretten geraucht; entsprechend sind über 90% der histologischen Typen der Gruppe Kreyberg I zuzuordnen.

Raucher der Gruppe „Stein" weisen nach Adjustierung von Berufsdauer, Rauchgewohnheit (TEW) und Alter gegenüber Rauchern der Gruppe „white collar" ein (sig.) doppelt so hohes Lungenkrebsrisiko auf; ein beträchtliches Überschußrisiko, das mit R = 2,7 sowie R = 2,6 für eine Berufsdauer von 11–20 Jahren bzw. 21–30 Jahren die höchsten Werte erreicht. Eine kanzerogene Wirkung der unspezifischen Staubbelastung selbst, wie sie für das Untersuchungskollektiv angenommen werden kann, ist nicht als Ursache dieses berufsbedingten Risikos anzunehmen (im positiven Fall wäre eine größere Zahl von Niemalsrauchern zu erwarten), vielmehr ein durch die Staubbelastung ausgelöster Prozeß, der die Wirkung des Tabakrauchens verstärkt.

Folgende Erklärung bietet sich an:

Das Bronchuskarzinom tritt am häufigsten in den zentralen Atemwegen auf. In diesem Bereich ist die größte Schadstoffbelastung pro Fläche (Zelle) anzunehmen, sie nimmt in Richtung periphere Atemwege ab, bedingt durch die Zunahme des Gesamtquerschnittes der Atemwege. Staubexposition sowie Tabakrauchen verursachen Small Airways Dysfunction/Disease, chronische Bronchitis, Emphysem, wobei es schon frühzeitig zu einer Zunahme des peripheren Atemwegwiderstandes kommt (Übersicht bei 4). Daraus resultiert eine Abnahme des Verdünnungseffektes und damit ein Anstieg der Schadstoffkonzentration in den zentralen Atemwegen. Es ist vorstellbar, daß durch Zusammenwirken von Staub und Tabakrauch der Prozeß in den peripheren Atemwegen verstärkt bzw. beschleunigt wird. Folgerichtig ist bei einem Raucher mit Staubbelastung die Schadstoffbelastung durch Zigarettenrauch größer als bei einem Raucher mit identer Rauchgewohnheit, jedoch ohne Staubbelastung; entsprechend nimmt das Lungenkrebsrisiko zu.

Aus präventivmedizinischer Sicht zeigt die vorliegende Analyse, welche Bedeutung für die Senkung des Lungenkrebsrisikos Maßnahmen zur Verminderung der unspezifischen Staubbelastung am Arbeitsplatz zukommt (folgerichtig auch für andere Erkrankungen). Weiters läßt sich ableiten, daß die Erhaltung der Tabakabstinenz bzw. deren Wiedererlangung für Angehörige „sensitiver" Berufe von großer Bedeutung ist. Völlige Tabakabstinenz oder zumindest Tabakabstinenz am Arbeitsplatz sind

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daher Arbeitsschutzmaßnahmen gleichzusetzen. Dies sollte in „sensitiven" Betrieben in Form von Gesundheitsinformation und Möglichkeiten der Raucherberatung (Raucherentwöhnung) berücksichtigt werden.

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KARCH, N.J.

"EXPLAINING THE URBAN FACTOR IN LUNG CACNER MORTALITY (A REPORT TO THE NATIONAL RESOURCES DEFENSE COUNCIL (III LUNG CANCER ATTRIBUTABLE TO TOBACCO USE))"

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A statistical problem in relating exposures during pregnancy and length of gestation. S. Samuels* and G. Lemasters (NIOSH, Cincinnati, OH 45226).

Exposures to DDT, lead, alcohol, and cigarette smoking have been linked to short gestational length. An interesting problem arises when preterm delivery is related to exposures which accumulate over time. Longer pregnancies have more opportunity for exposure in a cohort of pregnant workers; some pregnancies may be terminating while others are still adding to their exposure. If enough women work late in pregnancy, the largest final cumulative exposures may be associated with the oldest gestational ages purely as an artifact. In this paper, several techniques, including a variant of the Cox life table regression model, are employed to overcome this problem. These procedures all relate the chance of preterm birth at a given gestational age only to cumulative exposures up to that age. The Cox model has several other attractive features. The method allows one to model the time of preterm delivery, treating post-term deliveries as "censored". In addition, the method is based on ranks of delivery times and makes no parametric assumptions about the distribution of pregnancy length. These procedures are illustrated using a data set of over 1100 pregnancies from a recently completed occupational study. One important conclusion is that the method chosen should depend in large part on the quality of the data available.

Measuring exposure to tobacco smoke in infants: nicotine and cotinine in urine and saliva. R. Greenberg* (U. of N. Carolina, Chapel Hill, NC 27514), R. Etzel, N. Haley and F. Loda.

Infants whose parents smoke have more lower respiratory illness than infants of non-smokers. An objective, quantitative measure of an infant's exposure to tobacco smoke is needed to monitor the effectiveness of intervention programs. The authors studied the excretion of nicotine and its longer lasting metabolite cotinine by infants, using a radioimmunoassay. Urine and/or saliva were collected from 19 infants with no reported exposure within the previous week and from 32 with at least two exposures within the previous 24 hours. The infants were under 10 months of age and attending primary care clinics. Mean nicotine and cotinine concentrations in urine and saliva from exposed infants were significantly greater ($p < 0.001$) than from non-exposed. The best indicators of chronic exposure were the urine cotinine to creatinine (ng/mg) ratio (mean exposed, 459; mean non-exposed, 19) and the saliva cotinine concentration (mean exposed, 10.5 ng/ml; mean non-exposed, 0.2 ng/ml). There was a direct relationship between cotinine excretion and number of cigarettes consumed daily by the mother. Acute exposure might best be measured by saliva nicotine (mean if exposed within the previous hour, 43.3 ng/ml; mean if exposed earlier, 14.5 ng/ml ($p = 0.03$)). Levels of nicotine and cotinine from some infants were comparable to those found in actively smoking adults. This is the first reported study of a laboratory measure of infant passive smoking.

The epidemiology of the menopause. S. Standfast,* V. Kirmss, B. Pasley and P. Gould (NYS Dept. of Health, Albany, NY 12237).

There have been few population studies of the menopause in the United States. The study reported here of women aged 40–59 years looked at symptoms and patterns of health care related to menopausal status, knowledge, and attitudes related to menopause, estrogen use and endometrial cancer, and pertinent socioeconomic variables. The Gallup Organization used random digit dialing to contact a probability sample of 1028 women (response rate, 72%) in 13 upstate New York counties. Of the total respondents, 30% were premenopausal, 13% perimenopausal and 57% postmenopausal (no period for one year); 23% had had an artificial menopause. The per cent of women reporting hot flashes ranged from 17% among premenopausal women to a peak of 40% in those who stopped menstruating naturally 2–3 years ago, declining to 21% among those with natural menopause 5 or more years ago. Other common complaints of early postmenopause (up to 2 years) were fatigue, pain or aching of muscles, joints or bones, insomnia, night sweats and parethesias. Fifty one per cent of the women saw a medical doctor for their complaints. Estrogen was prescribed for 11% of total respondents; 4.9% were current users. Hot flashes constituted the symptom for which estrogen was most prescribed. No risk of estrogen use was known by 35% of the respondents, 43% indicated cancer and 18% mentioned endometrial cancer. Primary sources of information on the menopause were reported as magazines 20%, talking to doctor 18%, reading books 16%, newspaper 13%, and pamphlets 11%. This population-based study will be used in educating women and physicians about the menopause rather than using the biased sample usually seen in doctor's offices.

Cancer
Chairman: R. Peters

Patterns of lung cancer risk by detailed cigarette smoking categorization. J. Lubin* and W. Blot (NCI, Bethesda, MD 20205).

A case-control study of lung cancer involving interviews with 7800 patients and 15,000 hospital-based controls was carried out in seven locations in Europe. The large size of the study enabled the most precise assessment to date of 1) the impact of filter cigarettes, 2) the relative importance of duration vs. intensity of use, 3) the differences in risk between males and females, 4) the effect of reducing or quitting smoking, and 5) the variation in risk by histologic type of lung cancer. Lifelong nonfilter smokers were at twice the risk of lifelong filter smokers after controlling for duration of smoking, but strong gradients were observed with increasing consumption for both types. The number of cigarettes smoked per day and the number of years smoked were independent risk factors whose effects combined in multiplicative fashion. Gradients in risk with years of use and amount smoked were similar in males and females among both filter and nonfilter smokers, suggesting that the two sexes respond nearly equally

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to equivalent tobacco exposures. Reducing the number of cigarettes per day, or switching to a filter or low tar brand, resulted in only a small decrease in risk compared to completely stopping smoking. The rate of decrease in risk with cessation was similar by type of cigarette and varied only slightly with years of use. There were dose-response relationships with consumption for all cell types, but the trends were greater for squamous and oat cell cancers than for adenocarcinomas.

Smoking and herpes simplex virus type 2 infection: effects on cervical dysplasia. R. Mayberry,* W. Winkelstein, Jr. (UC Berkeley School of Public Health, Berkeley, CA 94720) and J. Schachter.

To assess the hypothesis that cigarette smoke promotes the oncogenic expression of herpes simplex virus type 2 (HSV-2) in the development of cancer of the cervix, the exposure to HSV-2 and the smoking habits of 210 women with cervical dysplasia were compared with those of 317 unmatched controls who were attending women's clinics at the same medical center. The subjects had participated in a previous study investigating the importance of chlamydia and HSV-2 infections on cervical cancer. The history of cigarette smoking on each of the current study subjects was obtained through a mailed questionnaire. Using as the reference, women who do not smoke and who were unexposed to HSV-2, the crude risk (odds ratio) for HSV-2 exposed current smokers was significantly greater than unexposed nonsmokers and greater than the risk for exposed nonsmokers. When *the analyses were restricted to cases with histologically* confirmed severe dysplasia, carcinoma in situ, and microinvasive carcinoma, the crude risks of disease were as follows: 6.30 for HSV-2-exposed current smokers; 4.25 for HSV-2-exposed past smokers; 3.71 for HSV-2-exposed nonsmokers. The trend was statistically confirmed ($p < 0.025$) by the extension of the Mantel-Haenszel chi-square test of trend with one degree of freedom. Adjustment for sex-related variables and other variables separately did not alter the observed trend. Multiple logistic analyses are currently under way to simultaneously adjust for the effect of various extraneous factors.

Risk factors for testicular cancer in young men. L. Brown* (NCI, Bethesda, MD 20205), L. Pottern, R. Hoover, N. Javadpour, K. O'Connell and R. Stutzman.

An epidemiologic investigation of risk factors for testicular cancer in patients aged 18–42 years seen at three medical centers during 1976–1981 resulted in interviews with 271 testicular cancer cases and 259 other cancer controls. This large series of cases enabled analysis of a number of medical and demographic characteristics previously suggested as risk factors for testicular cancer in smaller studies. Consistent with other studies, a history of undescended testes resulted in a fourfold ($p < 0.01$) increase in risk for testicular cancer. However, this risk was positively related to age at correction, with relative risks (RR) of 1.0, 2.0, and 7.0 for patients whose maldescent was corrected at ages <6, 6–10, and >10 years, respectively. Also, for those cases with a single undescended testis, there was no indication of an excess risk in the contralateral testis. Initially, a 50% excess risk was found with a history of groin hernia; however, this was apparently due to the correlation of undescended testes with hernia since a history of uncomplicated hernia yielded a reduced risk (RR = 1.2). Contrary to other reports, the authors found no excess risk for testicular cancer associated with potential external means of elevating testicular temperature (e.g., wearing jockey shorts vs. wearing boxer shorts, or taking a bath vs. taking a shower). Information on a variety of other potential risk factors such as place of childhood residence, childhood illnesses, family history of related conditions, and cigarette smoking was collected and is presented.

Case-control study of childhood cancers in Utah. K. Schuman,* J. Gardner, J. Lyon and D. West (U. of Utah, Salt Lake City, UT 84132).

All cases of cancer diagnosed in Utah residents <10 years of age for 1966–1979 were identified through the Utah Cancer Registry ($N = 499$). Study cases were limited to white, singleton births born in Utah ($N = 419$). Birth certificates were obtained for 91% of the study cases, and two matching adjacent birth certificates were selected as controls for each case. Cases and controls were compared for parental characteristics of age, education, state of birth, and occupation. Reproductive characteristics, including birth weight, previous births, congenital malformations, and complications of labor and delivery, *were also evaluated. These characteristics were* analyzed by age at diagnosis, county of residence, site and histologic type, and stage. The trend seen for the entire United States of higher male than female rates was not observed, but, overall, the Utah incidence of these cancers was comparable to national figures. A consistent and significant trend was seen for maternal age at time of birth of the child who eventually developed cancer. Cancer risk was 50% higher in children whose mothers were age 30 years and over at time of birth. The leukemia/lymphoma risk was more than twofold higher for children of women over age 35 years, as compared to age 18 years or less at time of birth. Further detailed analyses are presented.

A case-control study of cancer of the nasal cavity and sinuses. L. Brinton,* J. Becker, W. Blot, R. Hoover and J. Fraumeni, Jr. (NCI, Bethesda, MD 20205).

In High Wycombe, England, and certain other areas, an increased risk of adenocarcinomas of the nasal cavity and sinuses has been noted among furniture workers and woodworkers. To examine this relationship in the United States and to clarify other risk factors for nasal cancer, a case-control study of 160 patients and 290 controls was conducted in North Carolina and Virginia. Employment in the furniture industry was not associated with squamous cell tumors, but increased the risk of adenocarcinoma by fivefold. Risks were excessive among those exposed to wood dust, with duration and latency effects supporting a causal role. Elevated risks among males

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VUTUC, C.

"TAR YIELDS OF CIGARETTES AND MALE LUNG CANCER RISK"

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Medizinische Klinik

ORIGINALARBEIT

A. Knoth, H. Bohn, F. Schmidt:
Filterzigaretten als Lungenkrebsursache
Med. Klin. 78 (1983), 25–28 (Nr. 1)

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Filterzigaretten als Lungenkrebsursache

Zusammenfassung

Die vorliegende Studie an 792 Patienten mit Bronchialkarzinom aus dem Raum Mannheim–Ludwigshafen–Heidelberg ergab unter anderem, daß 97,3% unserer Lungenkrebspatienten Raucher waren.
Das durchschnittliche Sterbealter der Filterzigarettenraucher lag – statistisch gesichert – um 1,6 Jahre niedriger als bei den Zigarettenrauchern ohne Filter. Da die durchschnittliche Latenzzeit als ein Parameter der kanzerogenen Aktivität einer Noxe gilt, sprechen unsere Befunde klar gegen eine geringere Gesundheitsschädlichkeit des sogenannten „Leichtrauchens" in Form von Filterzigaretten, zumal diese Lebensverkürzung festgestellt wurde, obwohl der durchschnittliche Tageskonsum der Raucher mit Filter um 4,6 Zigaretten täglich geringer war als bei den Zigarettenrauchern ohne Filter. Ebenso lag die Gesamtzahl der gerauchten Zigaretten bei den Filterrauchern um etwa ein Fünftel niedriger. Auch die Gesamtrauchdauer der Filterzigarettenraucher war mit durchschnittlich 40,5 Jahren deutlich kürzer als bei den Rauchern ohne Filter mit 43,1 Jahren. Ebenso hatten wesentlich mehr Filterzigarettenraucher das Rauchen für mehr als ein Jahr unterbrochen als Zigarettenraucher ohne Filter (23,2% bzw. 14,1%).
Diese Befunde werden als weiterer Beweis dafür betrachtet, daß durch das sogenannte Leichtrauchen die Gesundheitsschäden des Rauchens nicht wesentlich reduziert werden können.

Der vorliegende Beitrag ist eine Kurzfassung der wichtigsten Ergebnisse der Dissertation von Knoth u. Bohn [8] an der Forschungsstelle für präventive Onkologie, die von F. Schmidt angeregt und betreut wurde. Primäres Ziel dieser statistischen Untersuchung zur Ätiologie des Bronchialkarzinoms war die Prüfung der Frage, ob Filterzigaretten im Vergleich zu Zigaretten ohne Filter weniger gesundheitsschädlich sind.

Das Rauchen, besonders das Zigarettenrauchen, ist die wichtigste Ursache des Bronchialkarzinoms; an anderer Stelle hat einer von uns [13] mehr als 30 Argumente dargelegt, die daran keinen Zweifel mehr offenlassen.

Für 90% aller Bronchialkarzinome ist das Rauchen der entscheidende Faktor. Diesen Schluß erlaubt bereits die Studie von E.C. Hammond an 37000 „statistischen Zwillingen". Mit einem Anteil von fast 30% ist das Bronchialkarzinom auch bei uns an die Spitze aller Krebsformen bei Männern gerückt. Für die kanzerogene Wirkung des Rauchens stehen dabei die Gesamtzahl der gerauchten Zigaretten, die Inhalationstiefe und der Zeitpunkt des Rauchbeginns im Vordergrund. Weiterer Untersuchungen bedarf jedoch die Frage, ob sich das Lungenkrebsrisiko durch Reduzierung des Schadstoffgehalts von Zigaretten, die überwiegend durch Zigarettenfilter erfolgt, wesentlich vermindern läßt.

Rauchgewohnheiten von Bronchialkarzinom-Patienten analysiert

Wir werteten dazu etwa 150000 Krankenblätter der zehn Jahrgänge von 1967 bis 1976 aus vier Großkliniken im Raum Mannheim–Ludwigshafen–Heidelberg (Städtische Krankenanstalten Mannheim und Ludwigshafen, Thoraxchirurgische Klinik Heidelberg-Rohrbach und Medizinische Universitätsklinik Heidelberg) aus. Alle Fälle ohne histologische oder zytologische Sicherung der Diagnose Bronchialkrebs bzw. ohne eindeutige Klärung, ob ein primärer Lungentumor oder eine Metastase vorlag, wurden ausgeschlossen. Insgesamt wurden auf diese Weise 2367 primäre Bronchialkarzinome ermittelt. Leider waren die Angaben über die Rauchgewohnheiten in den Krankenblättern nur sehr lückenhaft. Deshalb wurden an die Angehörigen ersten Grades dieser verstorbenen Patienten Fragebogen mit insgesamt 52 Fragen nebst frankiertem Rückantwortumschlag und erläuterndem Begleitbrief verschickt. Die Fragen betrafen alle nach unserer heutigen Kenntnis potentiellen Kausal- und Kofaktoren für die Entstehung des Bronchialkarzinoms. Von den 2367 versandten Fragebogen kamen 827 zurück. Nach Ausschluß unzureichend beantworteter Fragebogen verblieben 792 für eine statistische Auswertung. Die Antworten wurden auf Lochkarten übertragen. Die Datenverarbeitung erfolgte zu-

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nächst für die einzelnen Fragen getrennt. Soweit es aufschlußreich erschien, wurden anschließend einzelne Fragen im Hinblick auf etwaige Korrelationen überprüft.

Rauchen ist die Hauptursache für Lungenkrebs

Von den 792 Bronchialkarzinomen entfielen 733 auf männliche und 59 auf weibliche Patienten. Nur 4,2% der Fragebogen wurden von anderen Angehörigen als Ehegatte, Sohn oder Tochter ausgefüllt. In 67,9% stammten die Angaben von den Ehegatten der verstorbenen Patienten, so daß wir annehmen dürfen, daß die Angaben über die Rauchgewohnheiten des Ehepartners realistisch sind.

Da die rauchenden Patientinnen – mit Ausnahme einer „Gemischtraucherin" – nur Filterzigaretten konsumierten, erlauben sie durch das Fehlen einer Vergleichsgruppe keine Aussage über eine eventuelle Abweichung des Krebsrisikos durch das Rauchen von Filterzigaretten. Unsere Schlußfolgerungen stützen sich demnach auf die Befunde an den 733 Bronchialkarzinompatienten männlichen Geschlechts, von denen 293 Filterzigaretten und 206 Zigaretten ohne Filter bevorzugt hatten. Der Rest rauchte „gemischt" bzw. Zigarren oder Pfeife. In die Auswertung über die eventuelle Wirkung des Filters wurden die „Gemischtraucher" nicht einbezogen.

Der erste bemerkenswerte Befund war, daß 97,3% der Bronchialkrebspatienten Raucher waren. Dieser Prozentsatz stimmt mit internationalen Forschungsergebnissen weitgehend überein. Er ist ein weiterer Beleg für die überragende Rolle des Rauchens als Lungenkrebsursache, zumal Hinweise auf besondere berufliche Kanzerogenexposition weder bei den männlichen noch bei den weiblichen Patienten ermittelt werden konnten. Dies ist auch ein zusätzlicher Beleg dafür, daß industrielle Emissionen und Luftverunreinigungen durch den Autoverkehr als Bronchialkrebsursache deutlich zurücktreten. Zu der gleichen Schlußfolgerung kam im übrigen u.a. auch Ulmer [15] in seiner soeben erschienenen Monographie über den Stadt-Land-Faktor beim Bronchialkarzinom im Ruhrgebiet.

Filterzigarettenraucher konsumierten weniger Zigaretten

Bemerkenswerterweise bestanden bei den rauchenden Patienten deutliche Unterschiede in den Rauchgewohnheiten nicht nur hinsichtlich der Bevorzugung von Zigaretten mit oder ohne Filter: Die Raucher von Filterzigaretten rauchten im Mittel mit 26,4 Zigaretten täglich deutlich weniger als die Zigarettenraucher ohne Filter mit durchschnittlich 31,0 Zigaretten pro Tag. 95% aller Filterzigarettenraucher konsumierten zwischen 24,6 und 28,3 Zigaretten täglich. Dagegen hatten 95% der Raucher filterloser Zigaretten einen Tageskonsum von 28,4 bis 33,7 Stück.

Raucher ohne Filter rauchten nur in 7,8% zehn oder weniger Zigaretten. Bei den Filterrauchern waren es dagegen mit 17,4% mehr als doppelt soviel. Mehr als 41 Zigaretten rauchten nur 4,8% der Filterraucher, dagegen 8,3% der Raucher ohne Filter.

Das bedeutet: Eine vergleichende Gegenüberstellung von Zigarettenrauchern, die sich auf das Rauchen von Zigaretten mit und ohne Filter beschränkt, ist unzulässig. Diese Fehlerquelle ist in den meisten älteren Untersuchungen unberücksichtigt geblieben, aus denen eine geringere Gesundheitsschädlichkeit von Filterzigaretten abgeleitet wurde (zum Beispiel [4–6]). Wahrscheinlich wären die Unterschiede zwischen Rauchern mit und ohne Filter noch wesentlich größer, wenn man auch die Inhalationsgewohnheiten berücksichtigen würde. Leider besteht diese Möglichkeit bei retrospektiven Studien nicht. Die unterschiedlichen Rauchgewohnheiten von Rauchern mit und ohne Filter scheinen auf ein höheres „Gesundheitsbewußtsein" der Filterzigarettenraucher hinzuweisen – sofern man bei Rauchern von Gesundheitsbewußtsein überhaupt sprechen kann; vermutlich ist in dieser Einstellung – der Hoffnung, durch „Leichtrauchen" das Gesundheitsrisiko zu vermindern – auch die Hauptursache für die Bevorzugung von Filterzigaretten durch diese Gruppe unserer Patienten zu suchen. Darauf scheint auch hinzudeuten, daß der Anteil der Filterzigarettenraucher, die das Rauchen für mehr als ein Jahr unterbrochen hatten, mit 23,2% gegenüber 14,1% bei den Rauchern ohne Filter deutlich höher war.

Als Maßstab der kanzerogenen Aktivität einer Noxe gelten vor allem drei Kriterien:

a) Die Höhe der zur Krebserzeugung erforderlichen Dosis,

b) der Anteil der an Krebs Erkrankten,

c) die durchschnittliche Latenzzeit bis zur klinischen Manifestation bzw. bis zum Ableben des Patienten.

Hinsichtlich des Prozentsatzes der Erkrankungen an Bronchialkarzinomen bei Zigarettenrauchern mit und ohne Filter erlaubt die vorliegende Studie durch die erwähnten abweichenden Rauchgewohnheiten in beiden Gruppen keine eindeutige Aussage, wenn man davon absieht, daß daraus klar hervorgeht, daß eine „grobe" vergleichende Gegenüberstellung der Bronchialkarzinomhäufigkeit bei Rauchern mit und ohne Filter zu falschen Schlußfolgerungen führen muß und deshalb unzulässig ist.

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A. Knoth, H. Bohn, F. Schmidt:
Filterzigaretten als Lungenkrebsursache
Med. Klin. 78 (1983), 25–28 (Nr. 1)

Kürzere Zeit bis zur Krebserzeugung bei Filterzigaretten

Eine klare Aussage erlauben dagegen unsere Auswertungsergebnisse hinsichtlich der durchschnittlichen Latenzzeit: Die Raucher von Filterzigaretten starben durchschnittlich im Alter von 60,6 Jahren, die Raucher ohne Filter dagegen erst mit 62,2 Jahren. Nicht die Filterzigarettenraucher lebten demnach länger, wie man hätte erwarten dürfen, wenn Filterzigaretten – wie die Industrie behauptet – weniger gesundheitsschädlich wären, sondern die Raucher ohne Filter. Der Unterschied von 1,6 Jahren erscheint auf den ersten Blick nicht sehr gravierend, ist aber eindeutig statistisch gesichert; 95% aller Filterzigarettenraucher starben im Alter von 59,6 bis 61,7 Jahren, 95% der Raucher ohne Filter dagegen zwischen 61,1 und 63,3 Jahren.

Dieses bedeutsame Ergebnis wird aber noch wesentlich eindrucksvoller, wenn wir folgende Befunde berücksichtigen:

1. Der durchschnittliche Tageskonsum der Zigarettenraucher ohne Filter war nicht niedriger, sondern – wie erwähnt – um 4,6 Zigaretten täglich höher als bei den Filterzigarettenrauchern.
2. Der durchschnittliche Gesamtkonsum an Zigaretten bis zur Krebsentstehung lag ebenfalls mit 379000 bei den Filterrauchern gegenüber 468000 bei den Zigarettenrauchern ohne Filter nicht etwa höher, wie aufgrund der verkürzten Latenzzeit im Fall niedrigerer Schädlichkeit von Filterzigaretten zu erwarten gewesen wäre, sondern deutlich niedriger.
3. Die Gesamtrauchdauer der Filterzigarettenraucher betrug im Durchschnitt nur 40,5 Jahre, für die Raucher ohne Filter dagegen 43,1 Jahre; 95% aller Filterzigarettenraucher hatten 38,0 bis 43,0 Jahre geraucht, 95% der Raucher ohne Filter dagegen 41,1 bis 45,1 Jahre. Auch dies ist das Gegenteil dessen, was im Fall geringerer Schädlichkeit von Filterzigaretten zu erwarten war.
4. Das gleiche gilt für den Anteil der Raucher, die das Rauchen für mehr als ein Jahr unterbrochen hatten: Er war bei den Filterrauchern mit 23,2% wesentlich höher als bei den Rauchern ohne Filter mit 14,1%.

Trotz angeblich verminderten Schadstoffgehalts nimmt die Zahl der Bronchialkrebs-Toten zu

Wir halten also fest: Wenn Filterzigarettenraucher trotz geringeren Tageskonsums, trotz niedrigeren Gesamtkonsums, trotz kürzerer Gesamtrauchdauer und obwohl sie wesentlich häufiger das Rauchen für mehr als ein Jahr unterbrochen hatten, statistisch gesichert früher ihrem Bronchialkrebs erlagen als Zigarettenraucher ohne Filter, ist die Frage berechtigt, wie diese Befunde mit der Behauptung der Zigarettenindustrie in Einklang gebracht werden können, die auf dem bundesdeutschen Markt befindlichen Zigaretten seien die „leichtesten der Welt", und ihr Schadstoffgehalt sei seit 1961 auf weniger als die Hälfte vermindert worden.

Wir haben keine Möglichkeit, diese Angaben der Industrie durch exakte Messungen nachzuprüfen. Skepsis erscheint jedoch schon im Hinblick auf den hohen Marktanteil internationaler Zigarettenkonzerne auch auf dem bundesdeutschen Markt angebracht.

Selbst wenn die Angaben der Industrie jedoch stimmen, wäre dies aus folgenden Gründen praktisch weitgehend bedeutungslos, wie von Schmidt an anderer Stelle [10–12] überzeugend nachgewiesen wurde: Seit 1961 ist – trotz angeblich auf weniger als die Hälfte reduzierten Schadstoffgehalts bundesdeutscher Zigaretten – die Gesamtzahl der Lungenkrebstoten in der Bundesrepublik ständig weiter gestiegen und erreichte mit über 27000 im letzten, vom statistischen Bundesamt ausgewerteten Jahr ebenso einen neuen Rekord wie der Zigarettenkonsum 1981 mit über 129 Milliarden Stück. Es kann also nicht stimmen, wenn Dr. Feldgen als Sprecher der deutschen Zigarettenindustrie schon 1975 behauptete [5]: „Wir rauchen heute zwar doppelt so viele Zigaretten wie 1960 – nämlich 126 Milliarden Stück im Jahr – und nehmen trotzdem weniger Nikotin und Teerstoffe auf."

Das gleiche gilt für die „Trendanalysen über den Verbrauch von Nikotin und Rauchkondensat in der Bundesrepublik Deutschland" [14], die Timm im Auftrag der Industrie 1976 zum dritten Male veröffentlichte und wie folgt zusammenfaßte: „Rechnet man diese Ergebnisse in Zigarettenäquivalente des Typs aus dem Jahre 1961 um, so entspricht der für 1975 ermittelte Konsum von 21 Zigaretten je Raucher nur einem Äquivalent von circa 10 Zigaretten aus dem Jahre 1961." Hier werden Schadstoffgehalt und Schadstoffaufnahme fälschlich als identisch betrachtet und völlig unzulässigerweise gleichgesetzt.

Schadstoffgehalt und Schadstoffaufnahme sind nicht das gleiche

Auch der Einwand, daß sich diese Schadstoffverminderung infolge der langen Latenzzeit des Bronchialkarzinoms noch nicht voll habe auswirken können, ist unzutreffend. Er wurde bereits eindeutig durch die Ergebnisse der 20-Jahres-Analyse an 40000 britischen Ärzten von Doll u. Hill [4] widerlegt: 3500 von ihnen gewöhnten sich von 1951 bis 1964 – also etwa dem gleichen Zeitraum wie zwischen 1961 und 1975 – unter dem Eindruck

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wissenschaftlicher Forschungsergebnisse das Rauchen ab. Parallel dazu sank die altersberichtigte Lungenkrebsrate britischer Ärzte von 1951 bis 1966 um rund ein Viertel, während sie bei der übrigen Bevölkerung in England im gleichen Zeitraum weiterhin stark anstieg. Wären demnach Schadstoffgehalt und Schadstoffaufnahme identisch, hätte sich die Zahl der Lungenkrebstoten bis 1975 – und erst recht bis 1981 – deutlich vermindern müssen, zumindest aber nicht zunehmen dürfen. Schon das ist ein eindeutiger Beweis dafür, daß Schadstoffgehalt und Schadstoffaufnahme nicht in einen Topf geworfen werden dürfen.

Noch überzeugender, daß durch „Leichtrauchen" das Problem der Gesundheitsschädlichkeit des Rauchens nicht gelöst werden kann, sind die Befunde von Harke [6]. Er war als Mitarbeiter des inzwischen geschlossenen Forschungsinstituts der Zigarettenindustrie sicher unverdächtig, der Kampagne für das Leichtrauchen in den Rücken fallen zu wollen. Anhand von Urinanalysen für Nikotin und seine Abbauprodukte fand er – in offensichtlichem Zusammenhang vor allem mit unterschiedlicher Inhalationstiefe – eine Schwankungsbreite im Verhältnis von 1 bis 350. Nicht der Schadstoffgehalt von Zigaretten ist demnach für die Gesundheitsschäden entscheidend, sondern die Inhalationstiefe. Selbst bei einer Reduktion des Schadstoffgehalts von Zigaretten auf weniger als die Hälfte würde eine (unbewußte) Erhöhung der Inhalationstiefe nur um 1% – um den „Nikotinhunger" des Rauchers zu stillen – ausreichen, um eine Schadstoffverminderung von Filterzigaretten auf die Hälfte zu kompensieren oder sogar zu überkompensieren.

Schmidt [11] zog daraus schon 1977 den Schluß, daß auf dem Wege des Leichtrauchens das Gesundheitsrisiko des Rauchens nicht wesentlich reduziert werden kann. Eine ganze Reihe seitheriger Untersuchungen kamen zu dem gleichen Ergebnis, zum Beispiel [1, 3, 7, 9, 16]. Eine Verminderung der Teerstoffe im Tabakrauch erscheint zwar in jedem Fall erstrebenswert, nicht jedoch des Gehalts an Nikotin, weil gerade er für die Beibehaltung des Rauchens und auch für die Inhalationstiefe entscheidend ist. Die vorliegenden Ergebnisse sind für diese Auffassung ein weiterer eindrucksvoller Beleg.

Schon früher hatte F. Schmidt der Zigarettenindustrie geraten, nicht Zigaretten mit besonders niedrigem, sondern eher mit relativ hohem Nikotingehalt – bei niedrigen Kondensatwerten – auf den Markt zu bringen, um das Nikotinverlangen des Rauchers mit einem geringeren Tageskonsum an Zigaretten zu befriedigen.

Summary: Filter cigarettes as a causal factor of bronchial carcinoma

A study on 792 patients with bronchial carcinoma in the region Mannheim – Ludwigshafen – Heidelberg showed the following results: The death age of smokers consuming filter cigarettes was statistically significant on an average 1.6 years lower than of cigarette smokers without filter. The time of latency passes for a parameter of the carcinogenic activity of a noxious substance. Therefore our results contradict the assertion of lowered health damages by the so-called "light smoking" by filter cigarettes. This conclusion is supported further by the following statements: The shortened life expectancy was observed in spite of a lower daily consumption of the patients smoking with filter by 4.6 cigarettes on an average. Just so the total amount of smoked cigarettes by smokers with filter was by a fifth smaller. Furthermore the total duration of smoking of smokers with filter was 40.5 years and distinctly shorter in comparison to smokers without filter who smoked 43.1 years in the mean. In addition substantially more smokers of filter cigarettes had interrupted their smoking for more than one year than smokers without filters (23.2% resp. 14.1%). These results are considered as a further proof for the thesis that the so-called light smoking does not diminish the health damages of smoking substantially.

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PATTERNS OF LUNG CANCER RISK ACCORDING TO TYPE OF CIGARETTE SMOKED

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A case-control study of lung cancer involving interviews with 7,804 cases and 15,207 hospital-based controls was carried out in seven locations in Western Europe. The large study size permitted the calculation of precise estimates of the relative risk of lung cancer associated with smoking different types of cigarettes. Lifelong nonfilter smokers were at nearly twice the risk of lung cancer compared to lifelong filter smokers after controlling for duration of cigarette use and number smoked per day (RR = 1.7 for males and 2.0 for females). Lung cancer risks for filter, nonfilter and mixed smokers increased in proportion to intensity and duration of smoking and decreased with years since stopping smoking. The findings indicate that prevention activities should continue to emphasize smoking cessation, although switching to low-tar cigarettes may also yield some reductions in lung cancer risk.

In recent years several studies have suggested that the risk of lung cancer among smokers of filter (or low-tar) cigarettes is lower than the risk for users of nonfilter (or high-tar) cigarettes (Bross and Gibson, 1968; Dean *et al.*, 1977; Hammond *et al.*, 1976; Hawthorne and Fry, 1978; Kunze and Vutuc, 1980; Reid, 1966; Kunington, 1981; Vutuc and Kunze, 1980; Wynder *et al.*, 1970; Wynder and Stellman, 1979). Small numbers of cases in these studies, especially among lifetime filter smokers and among females, have often precluded a detailed evaluation of the risk reduction associated with filter cigarettes, or of the relationships between cigarette type and other measures of cigarette exposure. This paper presents results from a case-control study involving over 23,000 subjects, focusing on the differences in risk associated with nonfilter and filter cigarettes (and high vs. low-tar) and the comparative importance of intensity, duration and cessation of smoking each type of cigarette.

MATERIAL AND METHODS

During 1976-1980 lung cancer cases were drawn from hospitals at seven study centers in Western Europe (Table I). (Data collection in Rome was initiated 1 year later in 1977 and continued through 1980.) Although the types of hospital varied, all 6,920 male and 884 female cases were ascertained from admission records or through inquiries addressed to hospital staff. Upon identification of a suspected lung cancer patient, interviews were undertaken within the shortest possible time. Nearly all patients agreed to be interviewed. If the diagnosis was verified as primary lung cancer, the subject was retained as a case. In the rare instances when a subject was discharged from hospital prior to interview, no attempt was made to follow-up and the individual was omitted from the study.

Two controls were matched to each case by sex, age and study site. Controls were obtained by searching records of the various hospital units, then interviewed, usually a few weeks after the case. At several study sites matching was also carried out on hospital accommodation. For other sites this criterion was impractical, since accommodation was not related to socioeconomic status but to the physical condition or the medical treatment of the patient. Two controls could not be obtained for all cases, so that not all matched triples were complete.

During the first 6-12 months of the study, controls were accepted if they had no present or previous tobacco-related diseases. (Unacceptable control diseases included: cancers of the oropharynx, larynx, esophagus, pancreas, liver, kidney and bladder, myocardial infarction, stroke, peripheral vascular disease, aortic aneurysm, chronic bronchitis, emphysema, peptic ulcer, cirrhosis of liver, arteriosclerosis and other vascular diseases. This list was modified in 1977; see footnote to Table II). Because of the difficulty in locating suitable controls and their obviously reduced tobacco exposure, this criterion was changed in all areas except France, thus permitting patients currently admitted for a disease not considered to be tobacco-related to serve as controls. The change in the control selection criteria had a negligible impact on results because of the large study size and the small number enrolled during the start-up phase. In almost all areas controls also were matched to the case by hospital. However, because of the different health care delivery systems, with some hospitals being specialized oncology or pulmonary centers, some controls were recruited from nearby hospitals or clinics. In all, 13,460 male and 1,747 female controls were enrolled. The distribution of the control diseases is given in Table II.

All subjects were interviewed by trained interviewers using a precoded questionnaire. Due to design constraints (specialized hospitals, or cancer wards or floors) not all interviewers could be blinded to the

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TABLE I – SIZE OF STUDY POPULATION AND SOME CHARACTERISTICS OF ACQUISITION

Country	Sex	Cases	Controls	Characteristics of acquisition
Austria	M	1,580	3,160	Subjects from nine hospitals located throughout the country. Some controls selected from the practice of the referring physicians where most were undergoing general health examination
	F	250	500	
France	M	1,529	2,899	Subjects from 16 hospitals, 13 within the metropolitan area of Paris. Persons who had immigrated within the previous 10 years were excluded
	F	96	192	
Germany	M	392	721	Hamburg: Cases and controls obtained from two hospitals
	F	70	133	
	M	506	961	Heidelberg: Cases from a specialized hospital and controls from a nearby hospital or from among visitors to the hospital
	F	52	92	
Italy	M	1,115	2,123	Milan: For initial 3 years subjects from five Milan area hospitals (approx. half of all lung cancers). Afterwards study transferred to Varese Province, adjacent to Milan, where a registry was utilized to obtain nearly all incident cases
	F	87	172	
	M	1,141	2,282	Rome: subjects from nine largest hospitals. Data collection initiated 1 year after other sites
	F	103	206	
Scotland	M	657	1,314	Study covered all 11 major hospitals in Glasgow and surrounding areas
	F	226	452	
Total	M	6,920	13,460	
	F	884	1,747	

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subjects' status. However, because of the size and the multicentral nature of this study, quality control and interviewer comparability were emphasized continually. Interviewers were closely supervised and most worked for the duration of the data collection; the turnover rate was very low.

TABLE II – DISTRIBUTION OF CONTROLS BY DIAGNOSTIC CATEGORY

Disease category	Male	Female
Cancer of stomach	226	19
Cancer of colon/rectum	476	52
Cancer of prostate	150	0
Cancer of kidney[1]	32	1
Cancer of breast	22	167
Cancer of cervix	0	53
Cancer of skin, melanoma, basal-cell carcinoma	252	15
Leukemias	68	3
Lymphomas, Hodgkin's disease	253	38
Sarcomas	89	14
Other cancers (site specified)	432	94
Benign neoplastic disease, fibrocystic lesion	1,062	72
Fractures	897	77
Tuberculosis	1,092	86
Infective or parasitic disease	851	105
Diabetes mellitus	455	46
Anemia	106	29
Appendicitis, intestinal obstruction and hernia	633	59
Pancreatitis	96	4
Nephritis and nephrosis	201	25
Motor vehicle accidents	266	10
Myocardial infarction	89	5
Gastric ulcer[1]	86	3
Acute bronchitis	198	18
Nutritional and metabolic diseases	284	36
Chronic rheumatic heart disease	108	19
Hypertensive disease	306	50
Arteriosclerosis and other vascular diseases	248	23
Arthritis	48	9
GB and biliary duct disease and inflammation	469	102
Cirrhosis of liver[1]	105	4
Other non-neoplastic disease	3,880	509
Totals	13,460	1,747

[1] Control diseases acceptable until December 1977, and unacceptable after this date.

For each sex, analyses were based on estimates of relative risk (RR) within strata defined by study center and, where appropriate, by other factors. Summary RRs across strata and confidence intervals (CI) were obtained by the conditional likelihood method of Gart (1970). All RRs given in the Tables were adjusted at least for center. Tests for linear trend for variables with multiple exposure levels utilized the Mantel extension procedure (Mantel, 1963) with consecutive integers defining the ordered categories. For the tests of trend, p-values reflect one-sided probabilities. Additional analyses were carried out based on multivariate regression methods for matched data (Breslow *et al.*, 1978; Lubin, 1981); results closely paralleled the unmatched (stratified) analyses.

This paper focuses on the lung cancer association with filter and nonfilter cigarette use. Other analyses of risk patterns by cigar/pipe use, histologic typs and cessation of cigarette use are in preparation.

RESULTS

Table III shows that the ages at interview for controls were similar to those of cases, with the age distribution being similar for male and female cases. Cases had completed slightly fewer years of schooling and were less often ward patients. Only slight differences were observed by martial status, with males more likely to be married and females to be widowed.

The vast majority of respondents were cigarette smokers exclusively or had never smoked on a regular bases (Table IV). A total of 2.8% of the male cases and 19.4% of their controls never smoked, while for females the corresponding figures were 37.7% and 67.5%. Among males there was a 9.0-fold excess risk

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

TABLE III – DISTRIBUTION OF RESPONDENTS BY DEMOGRAPHIC CHARACTERISTICS

	Males		Females	
	Cases	Controls	Cases	Controls
Total number	6,920	13,460	844	1,747
Age at interview	%	%	%	%
<50	11	15	14	15
50-59	33	34	29	31
60-69	36	32	37	34
70+	19	20	21	21
Mean age	60.8	60.2	60.7	60.6
Years of schooling	%	%	%	%
0-8	55	50	41	41
9-12	34	33	54	47
13+	11	17	7	12
Mean years	8.0	8.5	8.5	8.6
Hospital status	%	%	%	%
Private	6	6	9	7
Semi-private	60	57	55	54
Ward	30	34	34	39
Out-patient	4	3	2	1
Material status				
Single	6	7	10	10
Married	83	80	57	62
Divorced	3	4	7	4
Separated	1	1	1	0
Widowed	7	8	26	24

of lung cancer with cigarette use, a slightly lower excess for cigarette and pipe (RR = 8.1) or cigar (RR = 6.9) use and an even smaller excess with exclusive pipe (RR = 2.5) or cigar (RR = 2.9) use. Among females, almost all smokers used cigarettes exclusively and were at a 3.9-fold excess risk. Subjects smoking pipes and/or cigars exclusively were omitted from the following analyses.

Data were obtained on smoking duration, number smoked per day and names of the four previous brands smoked. A large majority (62.5%) smoked one or two brands, while 87.1% consumed three or fewer; the remainder smoked four or more brands. When more than four brands were reported during the interview, most often consecutive brands were combined. Less frequently, if the smoker switched brands numerous times within a short period of time, years of use were summed and the cigarette brand was coded as mixed, or the four brands of longest duration were used. The coding procedure varied slightly by study site.

Filter vs. nonfilter users

On the basis of all brands smoked, subjects were categorized as lifetime filter, lifetime nonfilter or mixed users. The risk of lung cancer was higher among exclusive nonfilter smokers and mixed smokers than among lifetime filter smokers, after adjusting for cessation and either years of use or number per day (Table V). After adjusting simultaneously for years of use, number smoked per day, and years since cessation, smoking nonfilter cigarettes exclusively (or mixed brands) resulted in 1.7-fold (1.6-fold) excess risks for males and 2.0-fold (1.7-fold) excess risks for females compared to smoking filter brands exclusively.

Table V also shows RRs associated with duration and intensity of smoking each cigarette type, adjusting for time since cessation of cigarette use, since current smokers were more likely to be mixed or lifelong filter users. Among males the risks of lung cancer increased with years of use for all cigarette types, with the gradients not significantly different by type. There was more variability among females (where numbers were smaller): the risks increased with duration for filter and mixed smokers, but were variable for nonfilter smokers. Based on regression models, the gradients of increase with duration were only slightly greater in males than in females (but the differences by sex were statistically significant, $p<0.01$). The RRs also increased with number smoked per day for each cigarette type, but the gradients of increase for each sex were not significantly different by type.

For each type of smoker, RRs were cross-classified by duration and number per day (Table VI). Results are shown only for males, as data were insufficient for females. Among filter, mixed and nonfilter smokers, the risks increased with duration of smoking and number of cigarettes smoked per day within all categories of the other variable, thus suggesting separate effects. Based on a regression model for matched data, these variables (duration and number per day) combined in a fashion consistent with a multiplicative effect upon cancer risk.

Table VII shows RRs of lung cancer according to the proportion of time that nonfilter cigarettes were smoked (*i.e.*, years of smoking nonfilter cigarettes divided by total years of smoking). After adjustment for years of cigarette use, number smoked per day and years since cessation, there was a marked increase in risk among those who used nonfilter cigarettes, but only a small gradient among the mixed smokers with

TABLE IV – RELATIVE RISK OF LUNG CANCER BY TYPE OF TOBACCO PRODUCT USED

Type of tobacco product	Males			Females		
	Cases	Controls	RR	Cases	Controls	RR
Never smoked	3%	19%	1.0	38%	68%	1.0
Cigarettes only	87%	69%	9.0**	62%	32%	3.9*
Cigarettes and cigars	3%	3%	6.9**	0.1%	0.1%	3.3
Cigarettes and pipes	5%	4%	8.1**	0.1%	0%	—
Cigars only	1%	1%	2.9**	0%	0%	—
Cigars and pipes	0.3%	1%	4.6**	0%	0%	—
Pipes only	1%	2%	2.5**	0%	0%	—
Cigarettes, cigars and pipes	1%	1%	7.5**	0%	0%	—
Total number	6,919	13,458		884	1,747	

*p <0.05; **p <0.001.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

TABLE V – TRENDS IN RELATIVE RISK OF LUNG CANCER BY YEARS OF USE FOR LIFETIME FILTER, LIFETIME NONFILTER AND MIXED CIGARETTES SMOKERS. ALL RISKS ADJUSTED FOR YEARS SINCE CESSATION

	Males								
	Filter		Mixed		Nonfilter		Relative risks		
	Cases	Controls	Cases	Controls	Cases	Controls	Filter	Mixed	Nonfilter
Total No.	326	851	4,563	6,595	1,737	2,988			
Years of use									
1-29	37%	60%	11%	20%	19%	39%	1.0[1,2]	2.0[2]	2.5[2]
30-39	40%	27%	33%	36%	34%	29%	2.3	2.8	3.5
40-49	16%	9%	33%	28%	30%	21%	2.9	3.5	4.2
50+	8%	4%	22%	17%	17%	11%	2.8	3.6	3.7
Adjusted							1.0	1.6	1.8
95% CI								1.3-1.8	1.5-2.1
Number per day									
1-9	6%	17%	39%	48%	5%	15%	1.0[1,2]	3.2[2]	1.4[2]
10-19	26%	35%	21%	23%	28%	32%	2.0	3.7	4.6
20-29	36%	32%	26%	20%	38%	32%	2.6	5.9	5.5
30+	31%	16%	14%	10%	30%	20%	5.8	7.7	8.1
Adjusted							1.0	2.1	2.1
95% CI								1.8-2.4	1.8-2.5
	Females								
Total No.	102	184	393	330	56	53			
Years of use									
1-29	57%	65%	15%	26%	27%	47%	1.0[1,2]	1.8[2]	4.5[2]
30-39	28%	24%	36%	39%	30%	25%	1.5	2.6	4.1
40-49	10%	8%	33%	29%	27%	15%	1.5	3.0	6.9
50+	5%	3%	17%	6%	16%	13%	1.7	7.3	2.7
Adjusted							1.0	1.8	2.5
95% CI								1.3-2.6	1.2-5.2
Number per day									
1-9	19%	35%	32%	43%	11%	23%	1.0[1,2]	2.8[2]	1.6[2]
10-19	55%	39%	37%	36%	36%	42%	4.1	6.4	10.4
20-29	19%	17%	24%	17%	38%	30%	2.7	11.5	12.4
30+	8%	9%	7%	4%	16%	6%	2.8	26.3	34.7
Adjusted							1.0	2.3	2.3
95% CI								1.6-3.2	1.2-4.6

[1]Baseline exposure category. Risks of lung cancer for this category relative to non-tobacco users were: 1-29 years of use, 3.3 (males) and 1.9 (females); and 1-9 cigarettes per day, 2.0 (males) and 1.0 (females). – [2]Test of linear trend within cigarette type cytegory, $p < 0.001$.

the proportion of years during which nonfilter brands were consumed.

Smoking intensity factors

Table VIII shows that the risk of lung cancer decreased with years since cessation of smoking and increased with frequency and depth of inhalation after adjustment for duration of use for filter, mixed and nonfilter smokers. There were little or no differences in the gradients by cigarette type. These patterns were similar when further adjustment was made for number of cigarettes smoked per day.

The RRs for frequency and depth of inhalation were cross-classified by years of use and by number per day (Table IX). (Data are for combined cigarette types and are given for males only; results are similar for females, but more variable due to smaller numbers of subjects.) The risks with smoking intensity and years of use appeared to increase independently of each other: there was an approximately 3-fold increase from shortest to longest category of years of use and a 1.5-fold increase for the extreme categories of the intensity variables. This pattern was somewhat different when the inhalation factors were cross-classified with number of

TABLE VI – RELATIVE RISK OF LUNG CANCER BY YEARS OF USE AND NUMBER OF CIGARETTES PER DAY FOR LIFETIME FILTER, NONFILTER AND MIXED USERS. ALL RISKS ADJUSTED FOR YEARS SINCE CESSATION. MALE SMOKERS ONLY

Years of use	Number of cigarettes per day											
	Filter				Mixed				Nonfilter			
	1-9	10-19	20-29	30+	1-9	10-19	20-29	30+	1-9	10-19	20-29	30+
1-29	1.0[1]	3.1	3.7	9.6	1.0[1]	1.0	1.8	1.4	1.0[1]	1.7	2.1	3.2
30-39	5.1	6.7	10.4	30.2	1.4	1.6	2.2	2.7	1.1	3.5	4.3	4.6
40-49	14.0	19.3	17.5	20.5	1.9	1.7	2.6	4.1	0.6	3.5	5.0	7.2
50+	18.6	22.5	66.1	13.4	1.9	2.1	2.8	3.8	1.5	3.3	5.2	11.7

[1]Baseline exposure category. Among 1-9 cigarette per day 1-29 year users and after adjusting for cessation, the risks of mixed and nonfilter use relative to filter use were 3.7 and 3.8, respectively.

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

TABLE VII – RELATIVE RISK OF LUNG CANCER BY THE PROPORTION OF YEARS NONFILTER BRANDS WERE USED. ALL RISKS WERE ADJUSTED FOR YEARS OF CIGARETTE USE, NUMBER SMOKED PER DAY AND SINCE CESSATION

Proportion of years nonfilter brands smoked	Males	Females
0.00 (all filter)	1.0[1]	1.0[1]
0.01-0.49[2]	1.5	1.8
0.50-0.69	1.4	1.7
0.70-0.83	1.7	1.9
0.84-0.99	1.7	2.1
1.00 (all nonfilter)	1.7	2.0

[1]Test of linear trend, $p < 0.001$. – [2]Exclusive of 0 and 1. categories are tertiles.

cigarettes smoked per day. The gradient of increased risk with greater frequency and depth of inhalation was greater among those who smoked fewer cigarettes per day. Conversely, the risks with increased number per day had a steeper gradient among less intense smokers.

Tar levels

Current levels of tar were ascertained for all major cigarette brands (past levels generally were not available). The mean cigarette tar value was calculated for each smoker as the average tar value for all brands smoked, weighted by the number of cigarettes smoked per day, *i.e.*,

$$\Sigma_i\,(\text{No./day})_i \times \text{tar}_i/\Sigma_i(\text{No./day})_i$$

where summations are over all brands smoked. Since cigarette brands varied by country and tar measurements were carried out nationally, tar values were not comparable between countries. Therefore, six categories of cigarette tar level were defined within country by the 10%, 25%, 50%, 75%, and 90% quantiles then adjusted across study center. Keeping in mind the measurement differences, the mean tar values for the counties for each category were 15.6, 18.5, 20.6, 23.6, 25.2 and 29.8 mg. Excluded from the tar analysis were all respondents for whom a complete smoking history could not be obtained or any cigarette tar value was unavailable. Table X shows that the RRs, adjusted for years of use, number smoked per day and years since cessation, increased (although not smoothly) with mean tar value, with no significant difference in the trends by sex.

To examine the effects of years of smoking cigarettes at various tar levels, we ranked the cigarette brands within each country by current tar amounts and categorized them by tertiles into high-, medium- and low-tar brands. The number of years of smoking brands from each category was accumulated for each respondent. Among male smokers the cases averaged 28.8, 5.7 and 3.9 years using the high-, medium- and low-tar brands, respectively, while the corresponding control values were 24.5, 5.7 and 3.8 years. Among female smokers the mean years at successively lower tar levels were 20.7, 10.0 and 5.0 years for cases and 14.2, 10.8 and 5.4 years for controls. Table XI shows that after adjusting for years of cigarette use, number smoked per day and years since cessation, males who smoked the highest tar brands exclusively or for more than 75% of the time had a greater risk of lung cancer than those smoking predominantly the lowest tar brands, while those smoking cigarettes of mixed tar levels were at intermediate risk. Among females the patterns of risk were less consistent owing to small numbers, although the greatest risk occurred among the high-tar smokers exclusively. As can be seen from the Table, the type of cigarettes used differed markedly by sex. While 38.5% of all male users smoked the highest tar brands exclusively, 12.2% of the females did so. Among male smokers 10.9% never used the highest tar brands, compared to 33.0% among females.

DISCUSSION

The results of this large international investigation paralleled several other retrospective (Bross and Gibson, 1968; Dean *et al.*, 1977; Rimington, 1981; Wynder

TABLE VIII – RELATIVE RISK OF LUNG CANCER BY YEARS SINCE CESSATION OF CIGARETTE USE AND FREQUENCY AND DEPTH OF INHALATION. ALL RISK ADJUSTED FOR YEARS OF USE

	Males					Females				
	Cases	Controls	Filter	Mixed	Nonfilter	Cases	Controls	Filter	Mixed	Nonfilter
			RR	RR	RR			RR	RR	RR
Years since cessation										
0	71%	60%	1.0[1]	1.0[1]	1.0[1]	80%	72%	1.0[2]	1.0[1]	1.0
1-4	13%	10%	0.9	0.9	1.0	11%	10%	0.8	0.9	1.9
5-9	7%	9%	0.9	0.7	0.5	5%	7%	0.9	0.7	0.9
10+	9%	22%	0.4	0.5	0.3	4%	11%	0.3	0.2	0.4
Frequency of inhalation										
Rarely/never	10%	14%	1.0[1]	1.0[1]	1.0[1]	10%	21%	1.0	1.0[2]	1.0[3]
Part of the time	5%	6%	2.2	1.1	1.6	8%	10%	1.3	2.6	1.6
Most of the time	13%	14%	2.1	1.7	1.7	17%	15%	2.7	3.2	—
All of the time	72%	67%	2.4	1.8	1.6	65%	54%	1.6	3.5	2.7
Depth of inhalation										
Slightly/never	8%	10%	1.0[1]	1.0[1]	1.0[1]	21%	37%	1.0	1.0[3]	1.0[3]
Moderately	31%	31%	1.5	1.3	1.4	36%	39%	1.5	2.2	2.9
Deeply	53%	48%	2.1	1.9	1.7	43%	24%	2.6	4.5	2.5
Total[4]	6,630	10,439				551	567			

[1]Test for linear trend, $p < 0.001$. – [2]Test for linear trend. $p < 0.05$. – [3]Test for linear trend, $p < 0.01$. – [4]Due to incomplete data, the number of respondents varied slightly for each variable.

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TABLE IX – RELATIVE RISK OF LUNG CANCER BY YEARS OF CIGARETTE USE, NUMBER PER DAY AND INTENSITY RELATED FACTORS. MALE USERS ONLY

	Years of use				
	1-29	30-39	40-49	50+	Adjusted
Frequency of inhalation					
Rarely/never	1.0[1]	2.2	2.6	3.0	1.0[2]
Part of the time	1.6	2.4	3.3	3.1	1.4
Most of the time	1.3	3.0	3.7	4.6	1.7
All of the time	1.6	3.1	4.1	4.5	1.7
Depth of inhalation					
Slightly/never	1.0[1]	2.2	2.9	3.3	1.0[2]
Moderately	1.4	2.9	4.2	4.3	1.4
Deeply	1.8	3.2	3.8	4.6	1.7
	Number per day				
	1-9	10-19	20-39	40+	Adjusted
Frequency of inhalation					
Rarely/never	1.0[1]	2.5	4.0	5.1	1.0[2]
Part of the time	2.0	2.4	4.0	7.8	1.3
Most of the time	1.7	3.1	5.9	5.9	1.5
All of the time	2.0	3.6	4.9	6.4	1.4
Depth of inhalation					
Slightly/never	1.0[1]	2.5	3.5	4.8	1.0[2]
Moderately	1.6	2.5	4.5	4.6	1.2
Deeply	2.2	3.3	4.3	6.3	1.4

[1] Risk of baseline category for variables among 1-29 year relative to never smoked: frequency 3.1 and depth 3.1; and among 1-9 per day users frequency 3.3 and depth 3.9. – [2] Test of linear trend, $p < 0.001$.

TABLE X – RELATIVE RISK OF LUNG CANCER BY MEAN CIGARETTE TAR CONTENT. ALL RISKS ADJUSTED FOR YEARS OF USE, NUMBER SMOKED PER DAY AND CESSATION

Mean cigarette tar content[1]	Males			Females		
	Cases	Controls	RR	Cases	Controls	RR
I (lowest)	7%	10%	1.0[2]	27%	41%	1.0[2]
II	13%	14%	1.2	18%	14%	1.9
III	21%	16%	1.7	15%	11%	1.3
IV	38%	36%	1.3	28%	24%	1.1
V	16%	17%	1.3	9%	9%	1.5
VI (highest)	5%	7%	1.4	3%	1%	—
Total number	2,650	4,279		313	368	

[1] Categories were the within-country 10, 25, 50, 75 and 90th percentiles. Mean tar values within categories were 15.6, 18.5, 20.6, 23.6, 25.2 and 29.8 mg. – [2] Test of linear trend, $p < 0.01$.

et al., 1970; Wynder and Stellman, 1979) and prospective studies (Hammond *et al.*, 1976), which showed that, although risk of lung cancer was substantially greater among filter smokers than among nonsmokers, smoking filter cigarettes was associated with a smaller lung cancer risk than smoking nonfilter brands. A review by Lee and Garfinkel (1981) of studies addressing this issue indicated that filter smokers have a lung cancer risk which is 75% of the risk for nonfilter smokers. In our study, risks among filter smokers, adjusted for duration, number per day and cessation, were 59% (for males) and 49% (for females) of those of nonfilter smokers. The greater reduction may be due to our ability to define lifetime filter smokers, whereas other studies frequently relied on current or recent cigarette type and risks may have been affected by previous use of nonfilter brands. Because of the large number of respondents, we were able to show that the reduction in risk occurs for both sexes, even after adjustment for duration of use and number of cigarettes smoked per day.

Classification of brands into filter or nonfilter type has been used frequently as a convenient surrogate for cigarette tar exposure. However, due to improved filters and new tobaccos and blends, the amount of tar per cigarette has declined substantially over the years so that current nonfilter cigarettes often have less tar than previous filter brands (Maxwell, 1976; Wynder and Stellman, 1979). This means that epidemiologic investigations based on filter/nonfilter classification or current tar levels must be interpreted cautiously. Four studies have reported a substantial increase in risk with total tar intake (Hammond *et al.*, 1976; Joly *et al.*, 1983; Kunze and Vutuc, 1980; Vutuc and Kunze, 1980), although only Hammond *et al.* (1976) used historical tar values. [Two of these (Kunze and Vutuc, 1980; Vutuc and Kunze, 1980) were based on analyses of subsets of the data reported in this paper]. In this study we ranked each brand within country by tar content; in this way the risks were interpretable historically under the assumption that the *relative* tar ranks are unchanged. Our data showed that long-term smokers of the lowest tar brands were at about two-thirds of the cancer risk compared to long-term smokers of the highest tar brands. In these data the highest tar brands delivered about twice as much tar as the lowest brands, so that additional reductions can be expected with current low-tar brands, some of which contain less than one-fifth the levels of the highest tar brands.

Many reports have linked increased lung cancer risk with increased duration of cigarette use, number smoked per day and frequency and depth of inhalation [see the Surgeon General's Report (USPHS, 1982) for a review and references]. Few, however, have consid-

TABLE XI – RELATIVE RISK OF LUNG CANCER BY THE PROPORTION OF YEARS HIGH-, MEDIUM- AND LOW-TAR BRANDS WERE USED. ALL RISKS WERE ADJUSTED FOR YEARS OF CIGARETTE USE, NUMBER SMOKED PER DAY AND YEARS SINCE CESSATION

Proportion of smoking history[1]	Males			Females		
	Cases	Controls	RR	Cases	Controls	RR
Low-tar brands (100%)	3%	5%	1.0	3%	10%	1.0
Low-tar brands (>75%)	1%	1%	1.2	1%	3%	—
Other mixed levels	24%	40%	1.5	60%	58%	5.9
High-tar brands (>75%)	20%	15%	1.8	19%	16%	4.0
High-tar brands (100%)	38%	39%	1.7	14%	10%	7.7
Total number	2,650	4,279		313	368	

[1] Tar brand categories were less than 16.4 mg (low) and 19.2 mg or more (high).

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and the combined effects of these factors. Our data indicate that the deleterious effects of duration of use and number per day appeared to act multiplicatively, and the higher risk with nonfilter compared to filter use remained after adjusting for duration, number per day and cessation. The patterns of relative risks for frequency and depth of inhalation were similar within categories of duration but varied by number per day. In accordance with Doll and Peto (1976), who reported an effect of inhalation limited to light (less than 25 cigarettes per day) smokers, we found the increased risk associated with deep inhalation was greatest among those smoking the smallest number per day (although some excess risk was found in all inhalation groups).

Sources of possible bias needed to be considered in this study, since the multicenter design encompassing five European countries made some differences in survey methods unavoidable. The methods of case acquisition were similar among centers, with nearly all lung cancer cases admitted to the designated hospitals being included in the study. However, at several centers the location of the case within the hospital precluded interviewer blindness. Indeed, at two study sites specialized hospitals were utilized for case acquisition with controls obtained from a different hospital. Three points, however, argued against the interviewer's knowledge of patient status seriously influencing data collection: (1) the questions were of a closed form so that little interviewer discretion was possible; (2) being aware of this potential problem, interviewers were carefully instructed to avoid influencing patient response; and (3) the patterns of risks observed were similar between those centers where interviewers were blind to patient status and centers where they were not blind.

The differences in control selection procedures in this hospital-based study is of concern. Controls were hospital-matched, except as noted above, but there were differing distributions of admission diagnoses from center to center. All centers excluded as potential controls persons admitted for tobacco-related disorders. During the initial phase of the study, controls (but not cases) were restricted further to exclude those with a history of tobacco-related diseases, a procedure likely to result in an upward bias in the relative risk estimates, since tobacco use among those controls was likely to be low. This procedure was discontinued after 6 months at all but the French center. (The Rome segment of the study was initiated 1 year after the others, so that this additional control restriction was never implemented.) The change in the acceptable control criteria had no measurable effect on the risk estimates, however, due to the relatively small number of subjects enrolled during this start-up phase. (The RRs from the French data were elevated, but still within the range of all centers and showed similar trends to those seen elsewhere.) An additional concern of the control selection related to differences in the referral area for cases and controls, since cases may have been derived from a wider geographic area. Thus male cases were more likely to have been born or spent their childhood, teen or adult years in a rural environment. The RRs associated with residential history were small, with a maximum matched RR for rural vs. urban environment of 1.3, so that confounding by this factor did not seriously affect the RRs associated with the smoking variables. No residential differences were observed for females.

A problem in studies of well-publicized health associations, such as smoking and lung cancer, is recall bias, with cases more likely to remember cigarette exposure. This was not thought to be a major problem since the level of the awareness of the health issues surrounding smoking was high among both cases and controls. At the start of the interview, respondents were informed only that the survey was to gather general health information. In addition, the questionnaire was designed to assist recall by systematically moving from the most recent cigarette brand to the earliest. In any case, there would be no expectation that recall differences would occur for brand names, from which tar value and filter/nonfilter status were obtained. Further, although lung cancer patients may have been aware of some respiratory problems, it was not general medical procedure in these study areas to inform patients of their diagnosis.

In this report RRs were presented adjusted for study center. In general the risk patterns were similar for each center, differing at times only in the level of RR. A detailed evaluation of RRs by center is beyond the scope of this paper.

In summary, this case-control study, the largest of its kind, allowed detailed analysis of the relative effects of smoking filter and nonfilter cigarettes. Our findings indicate that lifetime filter smokers have a lower risk relative to lifetime nonfilter smokers than previously thought. Still, lifetime filter smokers are at a substantially higher risk of lung cancer compared to those who never smoked. For both filter and nonfilter smokers, risks increased with the intensity and duration of use. These findings indicate that smoking cessation must be the primary goal of efforts to prevent lung cancer, although changing to low tar (filter) cigarettes should help in reducing risk.

ACKNOWLEDGEMENTS

This study was carried out under contracts from the Office of Smoking and Health of the National Cancer Institute. Enviro Control, Inc. was the prime contractor for the initial 4½ years of data collection, with the Environmental Epidemiology Branch of the NCI monitoring the study for the remaining 6 months. We wish to thank Drs. G. Gori, D. Luecke and T. Owen of the NCI and Dr. C. Lynch and Ms. D. Potter of Enviro Control for their efforts in operation of the study and for facilitating transfer of the data to the NCI. We also thank Drs. J. Trauner, Jr., R. Hoover, E. Benhamou, E. Riboli and C, Vutuc and Mr. D. Hole for advice and assistance with these analyses, as well as Ms. Kandy Krump of ORI, Inc. and Mr. Peter Lee of the NCI for programming support.

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IN VITRO TRANSFORMATION OF RAT PLEURAL MESOTHELIAL CELLS BY CHRYSOTILE FIBERS AND/OR BENZO-3-4-PYRENE. M.C. Jaurand, M.J. Paterour, I. Bastie Sigeac and J. Bignon, Groupe de Recherches et d'Etudes sur les Affections Respiratoires et l'Environnement (INSERM U 139 et CNRS ERA n° 845), CHU Henri Mondor, 94010 Créteil Cedex, France

In vitro transformation of rat pleural mesothelial cells has been investigated using a two-stage model, with benzo 3-4 pyrene (BP) as initiator and chrysotile fibers as promoter. The criteria used to assess transformation were (i) the efficiency of cloning in liquid medium and (ii) altered colony morphology.

Exponentially growing cells were treated at 12th passage with 1 µg/ml BP (final DMSO concentration 0.05 %) for 48 hours. When confluent the cells were subcultured (weekly) ; following 27 subsequent passages, they were incubated with 2 µg/ml UICC A chrysotile fibers for 48 hours (BP-Ch). Controls were untreated (C) or treated with only BP (BP) or with 0.05 % DMSO followed by chrysotile (DMSO-Ch). 200 cells were plated per 60 mm dish ; classification of colonies was as follows : I, sparse criss-crossing ; II, overgrowth ; III, piling up.

The results show that the efficiency of cloning increased from 1 % at 12th passage to 35 % at 20th in treated an untreated cultures and thereafter remained nearly constant ; this was slightly lower in chrysotile treated cells than in other series. Transformed colonies were observed in every series ; the percentage of type II colonies was low until 29th passage (about 10 %). Type III was not found in untreated cultures (C), even after 40 passages ; oppositely, about 20 % type III colonies were observed in the 3 other series (BP, DMSO-Ch, BP-Ch) at the 33th passage, but the number of colonies was higher in BP treated cells than in DMSO-Ch or BP-Ch treated cells.

It could be concluded to an in vitro transformation of pleural mesothelial cells by chrysotile fibers or BP ; in these experimental conditions BP had a higher transforming potency than the fibers. In addition, chrysotile fibers did not potentiate BP activity.

A CASE-CONTROL STUDY OF INCIDENT MESOTHELIOMA DEATHS AMONG RAILROAD WORKERS. M.B. Schenker, E. Garshick, F.E. Speizer, Department of Internal Medicine, University of California, Davis, CA and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Recent reports have suggested that former railroad workers may have experienced clinically significant exposure to asbestos. We conducted a case-control study from March 1981 to February 1982 based on incident deaths occurring among current and former male railroad workers with ≥ 10 years of service and born > 1900. Cause of death was based on death certificate diagnosis and diagnoses were confirmed by review of pathologic material when possible. Cases were age matched to controls. Work histories were obtained from the Railroad Retirement Board and smoking histories from next-of-kin. Twenty incident deaths from mesothelioma occurred out of 15,000 deaths. Cases had a significantly (p<.001)greater history of job categories associated with work in railroad shops where steam engines had been repaired. Machinists appear to have the greatest increase in odds of developing mesothelioma. Review of historical work practices confirmed that most asbestos exposure occurred in areas of steam engine repair. A separate survey of 500 current workers provided additional data on previous asbestos exposure in the industry. Because we have collected total incident deaths for the entire period we are able to estimate the magnitude of risk of mesothelioma among current and previous railroad workers and potentially make predictions for the future.

Supported in part by Training Grant No. HL-07427 from the National Heart, Lung and Blood Institute and from the Environmental Protection Agency Grant No. R807515.

FIBER SIZE AND NUMBER IN AMPHIBOLE ASBESTOS-INDUCED MESOTHELIOMA. A. Churg, B. Wiggs, Department of Pathology, University of British Columbia, Vancouver, B.C.

We analyzed fiber size and number from the lungs of 10 patients who had an amphibole asbestos-induced malignant pleural mesothelioma. Amosite was found in 10 lungs and crocidolite in 9. On average amosite fibers outnumbered crocidolite by approximately 14:1. In the 8 patients who were not long time asbestos insulators, the mean number of amosite fibers was 2.8×10^6 fibers/gm dry lung, and of crocidolite fibers, 0.2×10^6/g. Crocidolite fibers were significantly narrower than amosite fibers (mean width 0.13 vs 0.23 µ), significantly shorter (mean length 4.0 vs 5.8 µ), and had a significantly higher mean aspect (length to width) ratio (48 vs 34). Aspect ratios in general increased with increasing fiber length and decreasing fiber width, but the highest values were found for thin amosite fibers at about 13 microns length, and thin crocidolite fibers at 8 or 15 to 17 microns length; longer fibers had lower aspect ratios. Comparison with data from other asbestos exposed populations indicates that mesothelioma can be induced by relatively small numbers of amphibole fibers, and also indicates that amosite is an effective mesothelial carcinogen in humans. Comparison of our data with epidemiologic and experimental predictions of carcinogenic size ranges implies that either the carcinogenic size range is much broader than has been assumed (and, specifically, is highly unlikely to be as small as 0.05 microns width or greater than 8 microns length), or, alternately, that extraordinarily small absolute numbers of fibers in certain size ranges can induce tumors in humans.

DETERMINANTS OF LUNG CANCER RISK IN CIGARETTE SMOKERS. J.M. Samet, D.P. Pathak, C.G. Humble, and B.J. Skipper, Departments of Medicine, and Family, Community, and Emergency Medicine, and the New Mexico Tumor Registry, University of New Mexico School of Medicine, Albuquerque, NM.

Although cigarette smoking has been causally associated with lung cancer, the effects of specific smoking practices have not yet been completely characterized. We have examined determinants of lung cancer risk in a population-based case-control study conducted in New Mexico, 1980-1982. The study included 521 cases and 769 age, sex, ethnicity matched controls, all interviewed in person to obtain a detailed history of cigarette smoking and information concerning other risk factors. Using multiple logistic regression, we modeled the effects of amount smoked, duration of smoking, cigarette type, and smoking cessation on lung cancer risk. In current smokers, relative risk increased exponentially with amount smoked ($p < 0.001$). While relative risk increased exponentially with duration of smoking in persons under age 65 years ($p < 0.001$), it did not do so in those 65 years and older. With regard to cigarette type, the modeling suggested protection by filter cigarettes, but the effect did not attain statistical significance. Lifelong filter smokers and smokers of both filter and nonfilter cigarettes were at lower risk than lifelong smokers of nonfilter cigarettes. In ex-smokers, the pattern of variation of relative risk with amount and duration was similar to that in the current smokers. Excluding those who had stopped for one year or less, the relative risk declined exponentially with duration of smoking cessation ($p < 0.01$). For example, the relative risk estimates, in comparison to current smokers of the same amount and duration, decline from 1.0 to 0.69, 0.33, and 0.11 with 5, 15, and 30 years of smoking cessation, respectively. These analyses confirm the strong benefits of smoking cessation and indicate possible protection from filter cigarettes. The varying effect of smoking duration with age suggests that other, unidentified factors, possibly host characteristics, interact with smoking to determine lung cancer risk.

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infection is not common in children presenting with enuresis,[2 3] there is a slightly increased incidence especially in girls[6] and we usually send a urine specimen for culture. Urine is also tested for glucose to exclude diabetes mellitus presenting with polyuria.

Some enterprising general practitioners have purchased enuresis alarms at their own expense to lend to patients. The time has now come when all general practitioners should be allowed to prescribe these useful devices. This would not only save drug dispensing and hospital costs but would be more convenient for patients and their parents—some of whom in our rural area face a return journey of over 100 miles to the outpatient clinic.

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Modifying risk of developing lung cancer by changing habits of cigarette smoking

SIR,—We regret to report a computer programming error which resulted in several incorrect numbers for tables IV-VII of our recent paper (30 June, p 1953). People for whom detailed cigarette smoking history was incomplete because of unknown cigarette brand, a brand which could not be classified as filter or non-filter, or unknown quantity information were incorrectly retained in the analyses. Thus the number of subjects with a complete historical smoking profile is fewer than was reported. The overall results, however, remain the same in the corrected tables, which we include here.

Similar to the original report, the revised table IV shows a significantly reduced risk among those who had stopped smoking (relative risk = 0·69), while among current smokers those who had reduced their cigarette consumption to less than one half their original number per day were not at lower risk (relative risk = 0·96) than those with a smaller reduction in intake (relative risk = 0·85). The risk in the corrected analysis continues to be significantly greater for those who had increased their daily cigarette consumption compared with those who had not altered their habit (relative risk = 1·22). Table V shows risks for those who had reduced their daily consumption, by years since the reduction, relative to those who had not changed habits. The corrected figures show clearer trends: in former smokers the gradient of the decrease in risk with years since the reduction occurred was slightly stronger than reported earlier (test for trend, $p < 0·001$); among current smokers there were moderate trends according to time since the reduction took place (tests for trend: 50% decrease or more, $p < 0·001$; less than 50% decrease, $p = 0·09$).

The greatest change in the corrected analysis occurs in table VI, where the percentage of people switching from filter to non-filter cigarettes is changed from 9% to less than 1%. The patterns remain the same, however, with the risks greater for lifelong smokers of non-filter cigarettes (current smokers: relative risk = 1·85, 95% confidence interval 1·5, 2·3; former smokers: relative risk = 1·56, 95% confidence interval 1·1, 2·2) and those who had switched from filter to non-filter brands (current smokers: relative risk = 2·24, 95% confidence interval 1·2, 4·1; former smokers: relative risk = 1·35, 95% confidence interval 0·4, 4·9) than for those who had smoked only filter cigarettes. Risks for smokers who had switched from non-filter to filter brands were raised compared with those subjects who had smoked only filter cigarettes (current smokers: relative risk = 1·58, 95% confidence interval 1·3, 1·9; former smokers: relative risk = 1·69, 95% confidence interval 1·2, 2·4). For smokers switching from non-filter to filter brands, table VII shows that the risks tended to decrease with years since the change (relative to smokers of filter cigarettes alone) but still remained 30-40% above those for subjects who smoked filter cigarettes exclusively, even after 20 years of filter use (tests of linear trends: current smokers: $p = 0·01$; former smokers: $p = 0·25$).

Remarkably, the substantive conclusions drawn from the revised tables are the same as from the earlier incorrect ones—even though the numbers of subjects are smaller. This was probably the result of the missing smoking profile data occurring unsystematically. Because of the error all other tables in the paper were rechecked and found to be correct as previously published. We regret this error and any inconvenience it might have caused.

TABLE V—*Relative risk* of developing lung cancer for subjects who decreased their daily consumption by years since decrease*

Years since decrease	Extent of decrease		
	100%	≥50%	<50%
1-4	1·0	1·5	0·8
5-9	0·7	0·8	0·8
10-14	0·6	0·8	1·2
15-19	0·5	0·5	0·7
20-24	0·4	0·7	0·7
≥25	0·4	0·7	0·6

* All risks relative to those who did not change.

TABLE VI—*Relative risks of developing lung cancer by most recent change in type of cigarette smoked. (All risks adjusted for duration of use in years)*

Type of cigarette	No (%) of patients (n = 4917)	No (%) of patients (n = 7696)	Relative risk*	Relative risk†
No change:				
Filter only	323 (6·6)	849 (11·0)	1·00†	1·00‡
Non-filter only	1740 (35·4)	2990 (38·9)	1·85	1·56
Filter to non-filter	40 (0·8)	55 (0·7)	2·24	1·35
Non-filter to filter	2814 (57·2)	3802 (49·4)	1·58	1·69

* Current smokers only.
† Ex-smokers only. Risks adjusted for time since stopping smoking.
‡ Baseline exposure. Risks of never smoked relative to filter only were 0·17 (current smoker) and 0·26 (former smoker).

TABLE VII—*Relative risk* of developing lung cancer since changing from non-filter brands of cigarettes*

Time since change (years)	Current smokers	Former smokers
1-4	1·8	2·7
5-9	1·6	1·5
10-14	1·6	1·8
15-19	1·3	1·9
20-24	1·3	1·6
≥25	1·4	1·5

* Risks relative to smokers of filter cigarettes only. Adjusted for years since stopping smoking.

Remarkably, the substantive conclusions drawn from the revised tables are the same as from the earlier incorrect ones—even though the numbers of subjects are smaller. This was probably the result of the missing smoking profile data occurring unsystematically. Because of the error all other tables in the paper were rechecked and found to be correct as previously published. We regret this error and any inconvenience it might have caused.

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*,*Our statistical adviser confirms that the conclusions of the study of Dr Lubin and others still stand.—ED, *BMJ*.

TABLE IV—*Relative risks for men of developing lung cancer by the percentage change in daily consumption (the most recent brand compared with the maximum daily consumption of earlier brands). Risk adjusted for duration of use in years*

Change in daily consumption	No (%) of patients (n = 4904)	No (%) of patients (n = 7696)	Relative risk	95% confidence limit
[illegible]e	1852 (37·7)	2497 (32·5)	1·00*	
[illegible]reased	1072 (21·8)	1174 (15·3)	1·22	1·1-1·4
Decreased:				
Stopped (100%)	1395 (28·4)	3173 (41·2)	0·69	0·6-0·8
Reduced (≥50%)	318 (6·5)	436 (5·7)	0·96	0·8-1·1
Reduced (<50%)	277 (5·6)	416 (5·4)	0·85	0·7-1·0
Total	1980 (40·5)	4025 (52·3)	0·73	0·7-0·8

* Baseline exposure. For men the risk of never having smoked relative to not changing number smoked per day was 0·10.

Induction of aneuploidy, a cluster of babies with Down's syndrome, and a potential danger with in vitro fertilisation

SIR,—As the high frequency of Down's syndrome in the babies of a small cohort of mothers who had previously attended a particular Irish boarding school is unlikely to have been due to chance alone (11 August, p 378) there has been some speculation on the underlying cause. I want to make two general points about the induction of aneuploidy by environmental factors and illustrate them with a particular example which coincidentally might have implications for another recent topic of correspondence—namely, in vitro fertilisation and the freezing of human embryos.

Although an apparent characteristic of aneuploid

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Lung Cancer:

Causes and Prevention

Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983

Edited by

Merle Mizell and **Pelayo Correa**

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CHAPTER 6

The Causes of Lung Cancer in Louisiana

PELAYO CORREA*, LINDA WILLIAMS PICKLE**, ELIZABETH FONTHAM*, NANCY DALAGER**, YOUPING LIN*, WILLIAM HAENSZEL,*** and WILLIAM D. JOHNSON*

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ABSTRACT

Lung cancer accounts for most of the excessive cancer mortality reported for Louisiana residents. A case-control study involving interviews with 1338 lung cancer patients and 1393 comparison subjects recently has been conducted. All newly diagnosed cases from all southern Louisiana hospitals as well as those from Alexandria and Shreveport hospitals were identified. Questions were asked about residential history, occupation, diet, smoking and drinking habits, source of drinking water, ancestry, income, education, and previous medical history. Preliminary results, including attributable risks for the main causative factors, are presented.

Key Words: **Forestry, oil/gas extraction, sugar cane, chemical manufacture, petrochemical manufacture, metal processing, shipbuilding, motor freight handling, wood dust, mineral oil, smoking, drinking water, fruit intake, vegetable intake, fishing, transportation industry**

South Louisiana has the dubious distinction of displaying some of the highest lung cancer rates in the country. Higher than average rates have been reported for approximately 50 years. Table 1 shows data for three time periods. In 1930–1932 Louisiana lung cancer death rates in males were higher than those for the United States. More recent data show that the excess has persisted. Rates in black males have surpassed those of white males. (1, 2).

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Table 1. *Lung cancer death rates in three time periods*[a]

Period/Population[b]	Louisiana	United States
1930–1932		
(adjusted to 1930 United States population)		
WM	4.0	3.1
WF	1.6	1.8
BM	1.9	1.4
BF	0.5	0.8
1950–1967		
(adjusted to 1960 United States population)		
WM	19.3	16.3
WF	1.8	2.2
BM	14.4	16.3
BF	1.5	2.2
1975–1977		
(adjusted to 1970 United States population)		
WM	81.8	66.2
WF	18.9	16.6
BM	82.1	77.2
BF	16.6	15.8

[a]Because of differences in population adjustment, rates can be compared only to each other within each time period.
[b]Abbreviations: WM, white *males*; WF, white *females*; BM, black *males*; BF, black *females*.

This type of clustering of cancer in the deltas of big rivers has been observed before, and hypotheses to explain its causes have abounded, mostly based on anecdotal thinking. A good example is provided by the conclusion reached by Alfred Haviland in 1875 after studying the geographic distribution of cancer in England (3):

> So, in cancer, the maps teach us that the high, dry sites on the older rocks are the places where cancer does not thrive, and that it does thrive in the vales by the sides of large rivers which overflow their banks, and in the neighbourhood of which are to be found the drifts of ages of washings from the inhabited country above. Where there is a tendency to cancer, let the patient be removed to the high, dry sites; and perchance if whole families were thus to emigrate, we should not hear so much of the hereditary character of this or of many other diseases.

Today, more than a century later, we still do not know whether the high frequency of cancer in the valleys near big rivers is due to river pollution as suggested by Haviland, to industrial occupational hazards, or to the lifestyle adopted by the inhabitants of those lands.

In an attempt to apply scientific methodology to study this problem, the National Cancer Institute and Louisiana State University have conducted a collaborative case–control study of lung cancer in South Louisiana. The same methodology has been applied in a smaller study in the north of the state, where cancer rates are lower, under the sponsorship of the Louisiana Chapter of the American Cancer Society. Preliminary results of these studies are reported here.

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Materials and Methods

Current primary lung cancer cases were identified from admission diagnosis and pathology records of all participating hospitals in 29 Louisiana parishes (counties) including all southern parishes plus one central (Rapides) and two northern parishes (Caddo and Bossier). All major hospitals in the study area participated except in the city of New Orleans where, for logistic reasons, interviewing was limited to two large hospitals serving the medically uninsured population and two large private hospitals. A control was randomly selected from patients attending the same hospital and matched to the case by race, sex, and age (within 5 years). Patients whose main diagnosis was emphysema, chronic bronchitis, chronic obstructive pulmonary disease, or cancer of the larynx, oral cavity, esophagus, or bladder were excluded from the control selection procedures. The admission diagnoses of the controls were distributed in the following categories: cardiovascular, 15.3%; gastrointestinal, 13%; musculoskeletal, 10%; genitourinary, 7.3%; ophthalmology and otorhinolaryngology, 6.6%; other tumors, 5%; diabetes, 5%; trauma 3.7%; peripheral vascular, 3.7%; pulmonary, 2.7%; cerebrovascular, 2.5%; infections, 2%.

Local professional interviewers, trained for this study and thoroughly familiar with the local culture, carried out personal interviews with the subjects (76% of the cases and 89% of the controls) or their next of kin. The questions covered occupation, residency, diet, smoking and drinking habits, health, water supply, and other related items. Histologic confirmation was obtained for 97% of the cases. Table 2 shows the number of acceptable completed interviews by sex, race, and location. An additional 34 cases of bronchioalveolar carcinoma were interviewed but are not included in the analysis.

Odds ratios were based on the products of the diagonals in 2 × 2 tables. Adjustments for smoking characteristics made by the direct method.

Table 2. Number of interviews[a]

	Cases	Controls
South Louisiana[a]		
WM	641	665
WF	201	217
BM	304	317
BF	73	75
Subtotal	1219	1274
North Louisiana[a]		
WM	62	62
WF	19	19
BM	29	29
BF	9	9
Subtotal	119	119
Total	1338	1393

[a] Abbreviations as in Table 1.

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Results

Smoking

Tables 3 and 4 show the odds ratio for each smoking category. The increase in risk with increasing amounts of cigarette use is evident in all sex–race groups. The results show the same general pattern observed in other studies, but the excess risk for each category of smoking when compared to that for nonsmokers is greater in Louisiana than in most other studies. The number of black females is admittedly small, and the results for them are unreliable.

Of the white male lung cancer patients, 97.7% were smokers. The corresponding figures for other race–sex groups were: black males, 97.6%; white females, 88%; and black females, 94%. Overall, fewer than 3% of males and about 10% of female lung cancer patients were nonsmokers.

Table 3. Odds ratios for lung cancer in Louisiana by pack-years of cigarettes smoked

	Odds ratio[a]			
Pack-years	WM	WF	BM	BF
0	1.0	1.0	1.0	1.0
1–20	3.6	1.5	4.0	13.3
21–40	9.5	7.7	14.6	19.5
41+	24.5	26.2	18.2	52.8
Total	17.2	8.6	13.1	22.0

[a]Abbreviations as in Table 1.

Table 4. Odds ratios for lung cancer in Louisiana by smoking characteristics[a]

	Odds ratio
Nonsmokers	1.0
Filter[a]	8.4
Nonfilter[a]	15.2
Age started[a]	
<16	24.2
16–20	17.4
21+	8.3
Current smoker	12.6
Quit	
3–5 years	7.7
6–20	7.0
20+	3.9
Inhale	
None	4.6
Mouth	6.3
Chest	11.3

[a]Adjusted for sex and age.

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Table 5. Lung cancer risk by social class (SC) and smoking categories

Category (pack-years)	Odds ratio	
	High SC	Low SC
Nonsmokers	1.0	0.90
≤20	2.79	4.28
21–50	9.44	11.84
51+	19.52	17.68

Increasing risks are seen for nonfilter versus filter cigarettes; earlier versus later starting age; nonquitters versus quitters, and deep versus light inhalation. The data for socioeconomic class suggest higher risks in the lower socioeconomic classes for light and moderate smokers but not for heavy smokers (Table 5). These results leave no doubt that smoking is the undisputed, overwhelming major cause of lung cancer in Louisiana.

Occupation

Odds ratios were calculated for all "ever employed" in occupation categories represented in our sample. Table 6 lists the results for occupations with elevated risks or occupations for which previous studies have suggested a positive association with lung cancer. Results are given for white males only because of small numbers and absence of positive associations for white females and blacks of both sexes. Only workers in the "forestry" category exhibited a significantly elevated risk; most of them were sawmill workers. After adjusting for smoking history, our study failed to detect any positive association with some Louisiana occupations previously suspected as playing a role in lung cancer causation, such as sugarcane farming, oil and gas extraction, construction, chemical manufacturing and processing, petrochemical manufacturing and processing, metal processing, and shipbuilding.

To enhance the possibility of detecting occupational effects that might not be uncovered by the summary classification of unusual occupations, we identified cases and controls who had worked in suspect occupations for 10 or more years and compared them with a selected group of cases and controls whose occupations suggested low exposure to carcinogens in the workplace (hunting and trapping,

Table 6. Odds ratio[a] for pertinent occupations, white males

Occupation	Odds ratio	
	Unadjusted	Adjusted for smoking
Forestry	1.56	1.67[b]
Petroleum refining	1.15	1.02
Printing	1.49	1.64
Fishing	1.72	1.20

[a]Never employed in the occupation = unit risk.
[b]Significant at 0.05 level.

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transportation and public utilities, wholesale and retail trade, finance, services, public administration). Included in this category were: professionals, technical, managerial, clerical, sales, amusement, recreation, and motion pictures. This group also excluded subjects who reported suspect exposures while employed in gasoline service stations, laundry and dry cleaning businesses, electrical and electronic engineering, chemistry, and agricultural sciences, or as farm advisers, commercial artists, and painters. Even after this effort to maximize the case–control contrasts of occupations, only forestry and lumber manufacturing gave positive significant associations after adjustments were made for smoking. Suggestive, but not statistically significant associations were noted for construction, petroleum processing, transportation, and motor freight handling.

Occupational Exposures to Suspect Materials

A list of 46 suspect materials was covered by specific questions in the interview. Table 7 shows the exposures with positive or borderline findings. After adjustments are made for smoking, only wood dust and mineral oil mist carry a significant excess risk. Known lung carcinogens such as asbestos, nickel, and chromium, display elevated but not statistically significant risks in our series.

Living Near Industrial Plants

Table 8 reports the results of our inquiry concerning proximity of residence to an industrial plant. Of the many types of plants mentioned, lumber mills and petroleum refineries showed a significantly elevated relative risk.

Drinking Water Source

Table 9 shows odds ratios for lung cancer by source of drinking water. Risks for persons born and currently living in locations served by surface water (S-S) did not deviate significantly from those born and currently living in locations served by ground water (G-G) (17).

Table 7. Odds ratio[a] for occupational exposures, white males

Material	Odds Ratio	
	Unadjusted	Adjusted for smoking
Wood dust	1.44[b]	1.40[b]
Mineral oil mist	2.10[b]	2.13[b]
Asbestos	1.30	1.30
Mustard gas	1.44	2.38
Nickel	1.44	1.89
Chromium	2.28	2.40
Cotton	1.42	1.70
Coal dust	2.02[b]	1.47
Lead	1.53	1.50

[a]Never exposed to the material = unit risk.
[b]Significant at 0.05 level.

Table 8. Odds rat

Plant
Any plant
Lumber
Petroleum refining
Chemical plant

[a]Resided two or more n
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Table 9. Odds ra

White males
White females
Black males
Black females
All subjects

[a]Persons born and resi

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Table 8. Odds ratio[a] of lung cancer for subjects less than 2 miles from industrial plants

Plant	Odds ratio	
	Unadjusted	Adjusted for sex, race, and smoking history
Any plant	1.17	1.28[b]
Lumber	4.25[b]	3.60[b]
Petroleum refining	1.21	1.47[b]
Chemical plant	0.86	0.90

[a]Resided two or more miles away = unit risk.
[b]Significant at 0.05 level.

Table 9. Odds ratios of lung cancer by drinking water source (S-S vs G-G)[a]

	Odds ratio
White males	0.99
White females	1.25
Black males	0.89
Black females	2.13
All subjects	1.02

[a]Persons born and residing in areas served by ground water supplies (G-G) = unit risk.

Nutrition

Detailed information was collected for 74 diet items. The intake of fresh fruits and vegetables was negatively associated with lung cancer risk. The foods that discriminated best between cases and controls were broccoli, lettuce, carrots, bananas, oranges, and fruit juice. To assess possible dose-response effects we created a composite index of fruit and vegetable consumption. For the 18 items in this category, intake was rated as low (<25 percentile), medium (25–74 percentile), or high (75 + percentile) based on the frequency distribution of consumption for individual foods. Values for 2, 5, and 9 were assigned for low, medium, and high exposure for each item.

Some results of this analysis are shown in Table 10. A clear enhancement of risk by low intake of fresh fruits and vegetables is seen, independent of cigarette smoking. The numbers of cases for some of the exposure combinations in the table are small and yield confidence limits that include unity. Inspection of this table, however, suggests that insufficient intake of fruits and vegetables increases lung cancer risk in light and moderate smokers. When the same kind of tabulation is restricted to the six items that seem to have a more pronounced effect as shown in Table 11 (lettuce, broccoli, carrots, bananas, oranges, and fruit juices) the effect is seen in all smoking categories. This suggests that the protective effect of fresh fruits and vegetables may be restricted to specific items. Further research is needed to clarify this point.

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Table 10. Odds ratios for lung cancer in white males of Louisiana by pack-years of cigarettes smoked and levels of consumption of fresh fruits and vegetables (18 items)

	Pack-years of cigarettes					
All fresh fruits and vegetables	0	1–20	21–40	41+	Crude	Adjusted for smoking
High	1.0	2.3	7.4	28.0	1.0	1.0
Medium	0.8	4.0	12.0	27.3	1.2	1.1
Low	1.9	6.5	11.4	31.9	1.6	1.3
Crude	1.0	3.8	9.9	26.8		
Adjusted for vegetables	1.0	3.6	9.7	26.6		

Table 11. Odds ratios for lung cancer in white males of Louisiana by pack-years of cigarettes smoked and levels of consumption of lettuce, broccoli, carrots, bananas, oranges, and fruit juices

	Pack-years of cigarettes					
Fruits and vegetables	0	1–20	21–40	41+	Crude	Adjusted for pack-years
High	1.0	3.1	12.2	28.5	1.0	1.0
Medium	1.5	5.8	15.6	36.6	1.5	1.3
Low	2.6	9.4	17.2	52.0	2.3	1.8
Crude	1.0	3.7	9.4	27.5		
Adjusted for vegetables	1.0	3.5	9.7	24.2		

Discussion

Alton Ochsner, to whom this volume is dedicated, correctly identified the beginning of the epidemic of lung cancer in Louisiana (4). His abundant clinical practice convinced him that cigarette smoking was the main reason for the epidemic. The high mortality rate for Louisiana was pinpointed by the National Cancer Institute (5) and specifically localized to the southern part of the state by the county maps (6). In 1975 Blot and Fraumeni (7) studied the correlation between industry and clusters of high lung cancer risk counties in Louisiana and other states and reported excessive rates for males in counties where paper, chemical, petroleum, and transportation industries were located. In 1977 DeRouen and Diem correlated parish-specific lung cancer rates with drinking water source information and reported a positive association between surface water and lung cancer rates limited to nonwhite males (8). After studying similar correlations for tumors of other organs, the authors dismissed the observation as nonspecific. Voors and co-workers did multiple regression analysis of lung cancer and environmental parameters and, in 1978 reported an association between lung cancer and residency in the wetlands, especially marked for South Louisiana (9). The relationship between lung cancer and nutrition has been explored by Lopez and his associates

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who, in 1979 and 1980, reported a negative correlation between lung cancer and β-carotene intake (10,11). Death certificates have been used extensively by Gottlieb and her colleagues (12–16). These studies have revealed an excess risk associated with shipbuilding, fishing, and oil-related industries. Acadian ancestry was associated with higher rates in older patients. These studies also revealed an association between surface water and lung cancer in nonwhite males only, as previously reported by DeRouen and Diem. This was again interpreted as artifactual, especially because the confounding effects of smoking and other environmental factors cannot be controlled in death certificate-based studies. Death certificate studies have been combined with next of kin interviews by Rothschild (17–19) and co-workers, who reported increased risks of lung cancer and mesothelioma in workers in the sugarcane industry. The same team described a continued rise in lung cancer rates in South Louisiana after the first report by Mason and McKay, later confirmed by Blot and Fraumeni (20). A study of histologic types by Rothschild and co-workers concluded that the distribution of histologic types was similar in low- and high-risk areas of Louisiana (19). Their findings are consistent with recent trends of decline in the proportion of squamous cell carcinoma and increase in the relative frequency of adenocarcinoma and small-cell carcinoma.

In terms of the magnitude of risks and the proportion of the population exposed to the risk factors cigarette smoking overshadows all other factors—occupation, air pollution, nutrition—considered in this report. The data in hand suggest that as much as 90% of all lung cancer cases in Louisiana are attributable to cigarette smoking. The second most important factor appears to be nutrition, which may be responsible for approximately 30% increase in the relative risk.

Our data in no way exonerate other factors as agents responsible for lung cancer deaths. One limitation of our study, shared by most studies available today, is that our controls are patients attending the hospital for other diseases. Both cases and controls are therefore "sick people" and no comparison to normal "healthy" subjects is made; this may obscure some of the etiologic associations. Some of the occupations and exposures listed in Tables 6 and 7, although not statistically significant, probably represent etiologic factors in lung cancer. Because some of them are avoidable by sound industrial hygiene practices, possible preventive programs should be designed and implemented. What our study indicates is that they are not responsible for a sizable proportion of the risk.

If prevention of the disease is contemplated, the strongest effort should be directed toward prevention of smoking. The second most important factor is nutrition, and more research is needed to evaluate the possible effects of improving the dietary intake of fresh fruits and vegetables.

Acknowledgments

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Lung Cancer:

Causes and Prevention

Proceedings of the International Lung Cancer Update Conference, held in New Orleans, Louisiana, March 3-5, 1983

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Merle Mizell and **Pelayo Correa**

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CHAPTER 7

The Causes of Lung Cancer in Texas

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ABSTRACT

A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties—Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria—to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950–1969 to 1970–1975 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents aged 30–79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment.

The exposures of primary interest in the study of lung cancer are those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures.

Key Words: Smoking history, petrochemical industry, histologic types, construction workers, chemical manufacturing, transportation

Introduction and Background

Data presented by Doll and Peto (1) and related reports (2) indicate that respiratory cancer sites, dominated by lung cancer, show the most dramatic increases of all cancer sites over the past 30 years. The role of smoking in the etiology of respiratory cancer has been well documented. In addition, lung cancer is

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recognized as possibly the most important work-related cancer. However, the interaction between smoking and occupational exposures and the increased risk that may be attributed to an occupational exposure has not been very well characterized for a large number of workplace exposures.

A population-based case-comparison interview study of lung cancer, obtaining detailed occupational histories, was conducted in six Texas coastal counties where lung cancer mortality rates were elevated (3). Figure 1 shows the location of the counties of Orange, Jefferson, Chambers, Brazoria, Galveston, and Harris, a highly industrialized area where Houston is located. Approximately 25% (3.5 million) of the total state population in 1980 resided in this southeastern coastal area, the majority (77.5%) in Harris County.

Newly diagnosed, histologically confirmed cases of lung cancer in white females (including Hispanic) were ascertained from July 1977 through June 1980 in Harris County (3 years) and from July 1976 through June 1980 for the surrounding five counties. Similarly, cases among white males (including Hispanic) were ascertained for four years (July 1976 through June 1980) for the five less urban but industrialized counties, excluding Harris County. Background lung cancer mortality rates for white males and females were examined by Texas State Economic Area

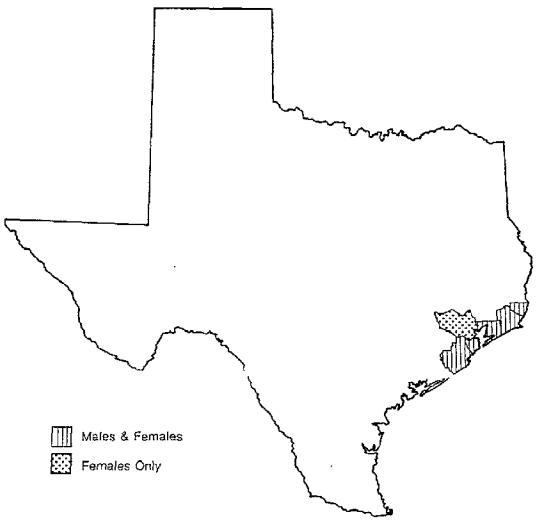

Figure 1. Texas lung cancer study area.

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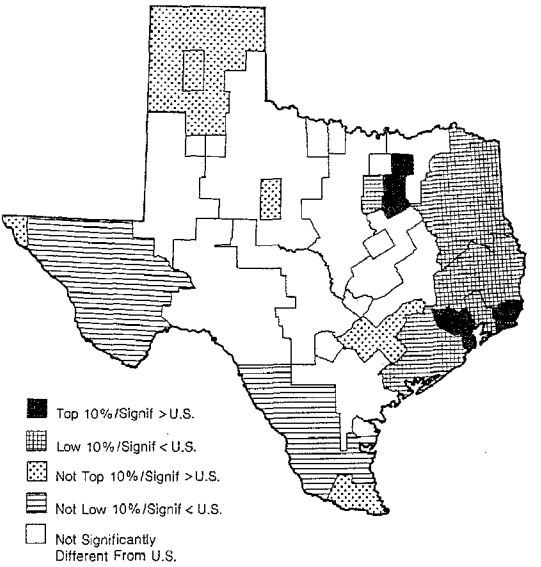

Figure 2. Lung cancer mortality 1970–1975 for white males.

(SEA) for the time period (1970 to 1975[1]) immediately preceeding the case-comparison study. As shown in Figures 2 and 3, these maps consistently document the significantly higher lung cancer mortality rates observed earlier for both white males and white females in these Texas coastal counties. The dark areas along the upper Texas coast are the Beaumont SEA (Orange and Jefferson counties), the Houston SEA (Harris County), and the Galveston SEA (Galveston County). Age-adjusted mortality rates (adjusted to the 1960 United States population) in these areas are in the top 10% of rates for SEAs in the United States and are significantly higher than the white male or white female lung cancer mortality rate for the total United States population. For white females in Harris County, this excess was notable for both the rate and the trend in the rate from 1950 to 1975 (4). For all ages, combined, the overall excess in lung cancer mortality in the Texas study area is approximately 30–40%, but this is considerably greater for some age groups.

Occupational and industrial exposures of importance for residents of the Texas coastal area include those associated with shipbuilding and repair, chemical and

[1]Excluding deaths for 1972.

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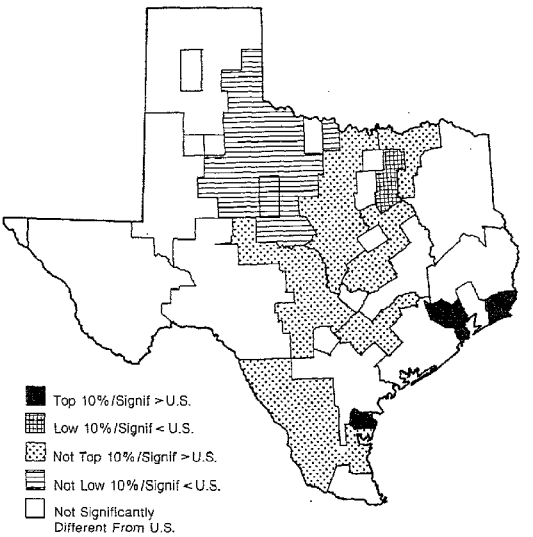

Figure 3. Lung cancer mortality 1970–1975 for white females.

petrochemical manufacturing, petroleum refining, construction, and metal industries. The largest United States based chemical and synthetic rubber production facilities are located in the study area, so a high proportion of the working population currently is employed or has been employed in these industries. For some of the smaller counties, such as Orange and Jefferson, where a single industry is dominant, as high as 27% of the working population reported being currently employed in chemical and allied products manufacturing compared with 2% for Harris County (5).

Methods

Histologically confirmed incident cases of lung cancer diagnosed among white male and female residents (including Hispanic) of the study counties for the designated time intervals (July 1977 through June 1980 for females in Harris County and July 1976 through June 1980 for males and females in other counties) were ascertained by review of hospital and state records. Hospitals in the study area that were not already participating in the Statewide Cancer Reporting Program

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were contacted and asked to participate in the study. Population-based and decedent comparison subjects were selected from state and federal records and matched to cases on age, race, sex, vital status at time of ascertainment, and county of residence (Harris County or other five counties). Hispanic study subjects were identified systematically by use of an algorithm to identify Spanish surname. Medical records were abstracted by state-trained abstractors to obtain relevant disease and demographic data. Following contact with the family physician (for cases only), personal interviews were conducted with study subjects or with the next of kin of decedent cases and comparison subjects, using established criteria for selecting the most appropriate next of kin respondents. Interviews were conducted by trained interviewers in the home using a standardized interview protocol. Detailed information regarding the primary exposures of interest was collected, specifically smoking history, work history, residential history, and drinking history.

Industries of employment were coded to the Standard Industrial Classification (SIC) (5) and occupations were coded using the *Dictionary of Occupational Titles* (7). The Mantel-Haenszel summary chi-square and odds ratio statistics were calculated (8). Confidence intervals (95%) were calculated using the method of Miettinem (9).

Results

A total of 56 of the 67 hospitals in the six-county Texas study participated in the study, including all of the seven large hospitals (500 or more beds). Ten of the 11 smaller hospitals that did not participate were located in Harris County. Therefore we were able to ascertain 92.2% (1520 cases) of the total 1649 incident white male and female lung cancer cases (including Hispanic) estimated for the 3- to 4-year interval (mid-1976 or 1977 to mid-1980). The number of incident cases was estimated by adjusting age-race-sex-county mortality rates by population growth and an incidence: mortality ratio of 1.35:1.0. Case ascertainment was higher for residents of counties other than Harris County, 97.2% vs 82.1% (Table 1). A total of 766 female and 754 male cases were ascertained representing, respectively, 88.7 and 96.1% of the total estimated incident cases ascertained. Hispanic females appear to be poorly ascertained (38.1%), but this may be related to the classification based on Spanish surname which may not be an effective technique for ascertaining married Hispanic females.

All ascertained cases will be used for determining age-race-sex and county lung cancer incidence rates for the study area. A total of 88.9% of the ascertained cases were included in the interview study. Some cases (110, or 7.2%) lacked histologic or cytologic confirmation of lung cancer and were ineligible for the case-comparison study. For the majority of these cases (79, or 71.8%) the basis of the lung cancer diagnosis was radiologic or clinical evidence. There was insufficient diagnostic information available on the remaining 31 cases. Additional losses of study subjects in the case-comparison study were related to race and residential eligibility criteria; unable to locate; moved out of interview area; physician,

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Table 1. Lung cancer case ascertainment in Texas study by sex, ethnic group, and area, 1976–1980

	Number estimated	Number ascertained[a] (%)	Number cases interviewed[b]
White Females			
Anglo	822	750 (91.2)	449
Spanish surname	42	16 (38.1)	11
Total	864	766 (88.7)	460
White Males			
Anglo	767	730 (95.2)	460
Spanish surname	18	24 (133.3)	15
Total	785	754 (96.1)	475
Area			
Harris County (females only, 1977–1980)	567	468 (82.1)	275
Other counties	1082	1052 (97.2)	660
Total	1649	1520 (92.2)	935

[a] Includes 110 cases without histologic confirmation and an additional 15 cases estimated to be ineligible, in terms of race and residence criteria.

[b] Excludes cases ineligible; not located; refusals by physician, hospital, or study subject; and cases interviewed and subsequently identified as ineligible, or data to be of poor quality.

Table 2. Texas lung cancer study population by sex, study group, and ethnicity

	Study group		
	Cases	Controls	Totals
Total			
Female	460	482	942
Male	475	466	941
Total	935	948	1883
Spanish surname			
Female	11	20	31
Male	15	19	34
Total	26	39	65

hospital, and subject refusals; and poor quality interview data. Overall study subject refusal rates were 7.7% and 10.7% for decedent cases and controls respectively, and 13.5% and 20.6% for living cases and controls, respectively. A total of 935 interviews was completed with eligible cases (460 females and 475 males) and 948 interviews with frequency matched comparison subjects (Table 2). Included in these totals are 26 Spanish surname cases and 39 comparison subjects. Separate analyses are not presented at this time for these study subjects.

The average duration of time study subjects resided in the county of diagnosis or in the six-county study area is over 25 years for all study groups. The majority of both male (86%) and female (82%) cases were decedent cases and were slightly older at time of diagnosis than the living cases (Tables 3 and 4). The distribution of age at diagnosis is compared for male and female study groups in Figure 4. A higher proportion of the female cases was diagnosed before age 60 (45.4%) than male cases diagnosed before age 60 (34%).

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Table 3. Number and percentage of male lung cancer cases by age at diagnosis and type of respondent, Texas, 1976 to 1980

Age at diagnosis (years)	Type of respondent: Self — Cases No	Cases %	Controls No	Controls %	Next of kin — Cases No	Cases %	Controls No	Controls %	Total — Cases No	Cases %	Controls No	Controls %
30–39	1	1.5	1	1.6	3	0.7	2	0.5	4	0.8	3	0.6
40–49	5	7.5	7	10.9	28	6.9	34	8.5	33	7.0	41	8.8
50–59	23	34.3	22	34.4	102	25.0	98	24.4	125	26.2	120	25.7
60–69	31	47.0	23	35.9	165	40.4	164	40.8	196	41.3	18.7	40.2
70–79 +	7	10.6	11	17.2	110	27.0	104	25.9	117	24.7	11.5	24.7
		100.0		100.0		100.0		100.0		100.0		100.0
Totals	67		64		408		402		475		466	

Table 4. Number and percentage of female lung cancer cases by age at diagnosis and type of respondent, Texas, 1976 to 1980

Age at diagnosis (years)	Type of respondent: Self — Cases No	Cases %	Controls No	Controls %	Next of kin — Cases No	Cases %	Controls No	Controls %	Total — Cases No	Cases %	Controls No	Controls %
30–39	0	0.0	3	2.6	6	1.6	5	1.4	6	1.3	8	1.7
40–49	9	11.1	12	10.3	40	10.6	50	13.7	49	10.6	62	12.9
50–59	36	44.4	55	47.4	118	31.1	104	28.4	154	33.5	159	33.0
60–69	24	29.6	34	29.3	153	40.4	135	36.9	177	38.5	169	35.1
70–79 +	12	14.8	12	10.3	62	16.4	72	19.7	74	16.1	84	17.4
		100.0		100.0		100.0		100.0		100.0		100.0
Totals	81		116		379		366		460		482	

Proportions of male and female cases and comparison subjects using tobacco, cigarettes, alcohol, or who "ever lived with household member who smoked regularly" are compared in Table 5. Ninety-seven percent of the male cases and 91% of the female cases reported ever smoking cigarettes but a higher proportion of the female than male cases reported smoking cigarettes currently, 68% vs 54%. Proportions of heavy smokers and use of alcohol (ever) were higher for cases than comparison subjects and for males than females. An extremely high proportion of both female cases and comparison subjects report having lived with a household member who smoked regularly, 93% vs 88%.

Although the patterns of risk differed for males and females (Table 6), the odds ratios for all smoking variables were statistically significant at the $p = .05$ level. Among males, ex-smokers had a risk higher than current smokers, whereas in females the risk was lower in ex-smokers. The highest odds ratio for females was observed for current smokers, 7.9 vs 5.0 for ex-smokers. Odds ratios for the ac-

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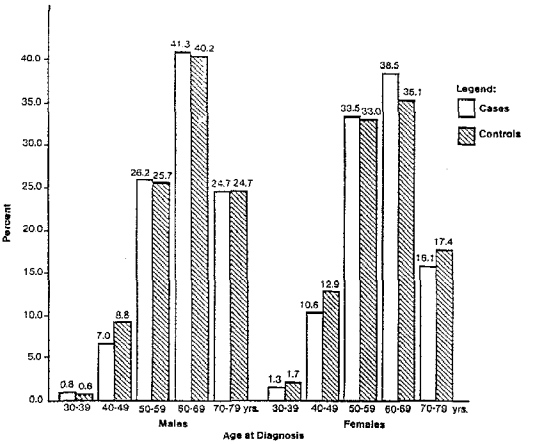

Figure 4. Age distribution (age at diagnosis) for male and female study subjects, Texas lung cancer study, 1976–1980. Clear columns, cases; shaded columns, controls.

cumulated lifetime cigarette dose, expressed as pack-years, were higher for males in the low and moderate categories but associated with a similar gradient in both males and females. No difference in risk was associated with the use of filtered cigarettes for either males or females.

The role of "passive smoking" in contributing to risk of lung cancer was examined (Table 7). In this analysis the crude (or unadjusted) odds ratio are increased and significant for both males and females, 1.4 and 2.1, respectively. However, when the confounding effect of individual subject smoking was controlled by stratifying the

Table 5. Proportion of cases and controls reporting use of tobacco, cigarettes and alcohol by sex, Texas lung cancer study, 1976–1980

	Males		Females	
	Cases	Controls	Cases	Controls
Tobacco (ever)	0.99	0.90	0.91	0.59
Cigarettes (ever)	0.97	0.80	0.91	0.59
Cigarettes (current)	0.54	0.47	0.68	0.38
Cigarettes (light)	0.08	0.10	0.08	0.17
Cigarettes (heavy)	0.45	0.29	0.34	0.13
Alcohol (ever)	0.86	0.81	0.78	0.63
Lived with a smoker	0.76	0.70	0.93	0.88

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Table 6. Odds ratios[a] associated with smoking variables for males and females, Texas lung cancer study, 1976–1980

	Males	Females
Ever smoked	10.12	6.89
Current smoker	9.59	7.89
Ex-smoker	10.85	5.00
Pack-years		
Low (0–35)	6.24	3.21
Moderate (36–63)	9.39	7.98
High (64 +)	13.05	13.35
Filtered cigarettes		
Yes	9.39	7.11
No	10.25	6.06
Both	12.27	7.09

[a]All odds ratios significant at $p < .05$.

male and female study groups into smokers (ever) and nonsmokers (never) and examining the adjusted odds ratios, there was no significant increase in risk associated with passive smoking. In fact, the odds ratios for nonsmokers living with a regular smoker were not increased for either males or females, 0.52 and 0.78, respectively. However, odds ratios for smokers living with a regular smoker were increased, although not significantly, 1.28 and 1.80 for males and females. The overall odds ratios (adjusted) associated with passive smoking were only slightly increased and not significant for either males or females, 1.2 and 1.3, respectively. When the possibility of a "passive smoking" effect was examined among nonsmokers by number of years lived with a regular smoker, there was very little difference in risk for females who lived with a regular smoker for 0-32 years (Table 8). The odds ratios for males suggest an increase by are based on smaller numbers than the analysis in females.

Table 7. Odds ratios for passive smoking (household member smoked regularly) in Texas male and female lung cancer studies, 1976–1980

	Yes		No		Odds	95%	
	Case	Control	Case	Control	ratio	Confidence interval	χ^2
Males							
Crude	363	329	93	119	1.41[a]	1.04, 1.92	4.8
Self ever smoked							
No	5	56	6	34	0.52	0.15, 1.74	1.2
Yes	357	273	87	85	1.28	0.91, 1.79	2.0
Overall (MOR)					1.20	0.87, 1.65	1.18
Females							
Crude	429	425	24	51	2.12[a]	1.29, 3.50	9.05
Self ever smoked							
No	33	164	8	32	0.78	0.34, 1.81	0.3
Yes	396	260	16	19	1.80	0.92, 3.58	3.0
Overall (MOR)					1.30	0.78, 2.18	1.0

[a]$p < .05$.

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Table 8. Odds ratios associated with passive smoking

Ever live with household member who smoked	Number	Odds ratio	Confidence interval	χ^2
Males				
Total nonsmokers	61	0.52	0.15, 1.74	1.2
0–32 years	49	0.40	0.10, 1.58	1.8
33+ years	10	1.56	0.30, 8.05	0.3
Females				
Total nonsmokers	201	0.78	0.34, 1.81	0.3
0–32 years	97	0.62	0.24, 1.63	0.9
33+ years	99	0.93	0.38, 2.28	0.0

Histologic types of lung cancer were classified according to the World Health Organization (WHO) classification (10). The four major cell types account for 75–85% of the cases in both the male and female series and the cell type distribution by age group is shown for males and females in Table 9. Adenocarcinoma is the predominant lung cancer cell type in both young (30–49 years) males and females, comprising 37.8% (males) and 38.9% (females) of all lung cancers among persons aged 30–49 years at diagnosis. There is a marked shift with age in this pattern such that for both males and females aged 70 or older at diagnosis the predominant cell type is squamous or epidermoid (accounting for 40.5% of all cases among males and 31.0% among females). Overall, squamous was the predominant cell type among males (42.2%) and adenocarcinoma among females (35.5%). These patterns held for both smokers and nonsmokers except for nonsmoking males, in whom 6 of 11 (54.5%) cases were adenocarcinoma.

The risk associated with smoking was examined by cell type, specifically odds ratios for smoking categories within the adenocarcinoma series compared with nonadenocarcinoma cases (Tables 10 and 11). The odds ratios for smoking categories based on pack-years were all significant, emphasizing the increased risk of lung cancer (all types) associated with smoking. However, the gradient of risk, in both males and females, was markedly different for adenocarcinoma compared with nonadenocarcinoma (all other lung cancer) cell types. There were 104 cases of

Table 9. Male and female lung cancer cases by histologic type and age, Texas, 1976–1980

	Males						Females					
	30–49 years		50–69 years		70+ years		30–49 years		50–69 years		70+ years	
Cell type	No	%	No	%	No	%	No	%	No	%	No	%
Squamous	8	21.6	112	34.8	47	40.5	11	20.4	74	22.6	22	31.0
Small cell	4	10.8	64	20.1	16	13.8	10	18.5	92	28.1	11	15.5
Adenocarcinoma	14	37.8	73	22.9	17	14.7	21	38.9	99	30.3	19	26.8
Large cell	2	5.4	19	6.0	9	7.8	4	7.4	11	3.4	3	4.2
Other		24.4		16.2		23.2		14.8		15.7		12.5
Total		100.0		100.0		100.0		100.0		100.0		100.0

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Table 10. Odds ratios associated with smoking for lung cancer cell types in males, Texas lung cancer study, 1976–1980

Cell type	Smoking category (pack-years)	Odds ratio	Confidence intervals	χ^2
Adenocarcinoma	Low	3.85	1.44, 10.31	8.04
	Moderate	4.45	1.72, 11.48	10.93
	High	5.38	2.14, 13.56	15.21
Nonadenocarcinoma	Low	6.60	2.75, 15.84	21.57
	Moderate	11.30	4.87, 26.19	43.75
	High	15.41	6.73, 35.25	63.34

Table 11. Odds ratios associated with smoking for lung cancer cell types in females, Texas lung cancer study, 1976–1980

Cell type	Smoking category (pack-years)	Odds ratio	Confidence intervals	χ^2
Adenocarcinoma	Low	2.16	1.18, 3.98	6.37
	Moderate	4.32	2.40, 7.79	26.11
	High	7.80	4.28, 14.20	52.93
Nonadenocarcinoma	Low	4.17	2.34, 7.43	25.80
	Moderate	10.97	6.27, 19.20	86.87
	High	18.90	10.61, 33.67	128.13

adenocarcinoma in the male series and 139 in the female series. A much steeper increase in risk associated with lifetime cigarette dose (pack-years) is observed for all other lung cancer cell types compared to adenocarcinoma. These patterns are summarized in Figure 5.

Preliminary analyses of the detailed work histories is based on the usual occupation and usual industry of employment as reported or as summarized from the work history for self and spouse. Examination of the work histories indicates that approximately 78% of the study subjects spent more than half of their reported working time employed in the occupation reported as their usual occupation. Usual industry of employment was determined by selecting the industry in which a subject was reported to have been employed for the longest duration of time. Odds ratios, adjusted for smoking (ever/never) were determined to identify whether an increased risk was associated with employment in a given occupation or industry for both males and females. Using the Professional/Technical category as a referent for males (odds ratio = 1), none of the odds ratios for the other occupational categories was significantly increased (Table 12). Odds ratios (OR) for usual industry of employment were similarly calculated using the sales category (SIC 50–59) as the referent (OR = 1.0) (Table 13). Significantly elevated odds ratios were observed for several industrial categories, specifically construction (SIC 15–17), chemical manufacturing (SIC 28), metal manufacturing (SIC 33–34), and transportation (SIC 40–49). In addition, an elevated odds ratio (OR = 2.44) of borderline statistical significance (at the .05 level) is observed for oil and gas extraction (SIC 13).

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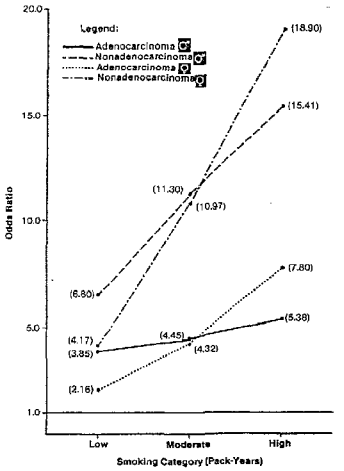

Figure 5. Odds ratios associated with smoking by lung cancer cell type.

The majority (approximately 60%) of the females reported their usual occupation as housewife. Using this category as the referent (OR = 1.0), smoking-adjusted odds ratios (ever/never) were calculated for the remaining categories (Table 14). Although there are several categories with elevated odds ratios, only the odds ratio for the clerical category (1.57) is significant. The odds ratio for the service category (1.57) is similarly increased, and of borderline statistical significance.

Table 12. Adjusted[a] odds ratios for usual occupation in Texas male lung cancer study, 1976–1980

Occupation category	Total number in category (cases and controls)	Odds ratio	Confidence interval	χ^2
Clerical/Sales	94	0.61	0.36, 1.04	3.33
Service	50	1.12	0.60, 2.09	0.13
Agriculture	39	0.89	0.44, 1.84	0.09
Processing	77	0.80	0.47, 1.38	0.63
Machine trades	77	1.37	0.78, 2.39	1.19
Bench work	14	1.04	0.34, 3.19	0.01
Structural work	275	1.46	0.96, 2.20	3.15
Miscellaneous	140	0.89	0.55, 1.44	0.22
Professional/Technical	157	1.00	— —	—

[a]Adjusted for smoking (ever/never).

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Table 13. Adjusted[a] odds ratios for usual industry of employment in Texas male lung cancer study, 1976–1980

Industry category (SIC number)	Total number in category	Odds ratio	Confidence interval	χ^2
Agriculture (01–09)	30	1.64	0.70, 3.83	1.31
Oil/gas extract (13)	28	2.44	1.00, 5.97	3.82
Other mining (10–12, 14)	8	0.72	0.19, 2.80	0.22
Construction (15–17)	150	2.56[b]	1.49, 4.41	11.50
Chemical (28)	60	2.16[b]	1.10, 4.24	5.04
Petroleum (29)	178	1.54	0.91, 2.60	2.63
Metals (33–34)	25	3.38[b]	1.36, 8.39	6.90
Shipbuilding (373)	27	1.91	0.83, 4.42	2.29
Other manufacturing (20–39 minus above)	52	1.55	0.77, 3.12	1.51
Transportation (40–49)	120	2.57[b]	1.47, 4.52	10.88
Personal services (60–69, 80, 91–97)	65	1.73	0.91, 3.29	2.76
Professional/Governmental (70–79, 81–87)	85	1.34	0.73, 2.44	0.91
Sales (50–59)	97	1.00	— —	—

[a]Adjusted for smoking (ever/never).
[b]$p < .05$

Table 14. Adjusted[a] odds ratios for usual occupation in Texas female lung cancer study, 1976–1980

Occupation category	Total number in category	Odds ratio	Confidence interval	χ^2
Clerical	161	1.57[b]	1.07, 2.31	5.27
Service	88	1.57	0.96, 2.57	3.22
Agriculture	3	0.74	0.14, 3.92	0.12
Processing	2	4.22	0.43, 41.33	1.53
Machine trades	2	2.66	0.45, 15.93	1.15
Bench work	11	1.67	0.47, 5.97	0.62
Structural	2	5.22	0.79, 34.59	2.93
Miscellaneous	8	2.27	0.52, 9.98	1.18
Professional/Technical	110	1.15	0.75, 1.76	0.40
Housewife	551	1.00	— —	—

[a]Adjusted for smoking (ever/never).
[b]$p < .05$

There were too few observations in the remaining categories for a meaningful analysis. A similar analysis of usual industry of employment for females indicated no categories of concern except for the possible exception of the increase noted for the category of other manufacturing (Table 15).

Smoking-adjusted odds ratios were also examined for the usual occupation and industry of employment for the spouses of both males and females. The only significantly increased odds ratio observed was for the usual industry of employment for spouses of female lung cancer cases. The Construction industry, with 146 cases and controls reporting this as the usual industry for their spouse, was associated with an increased odds ratio of 1.74 (1.04, 2.92; $\chi^2 = 4.40$).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Table 15. Adjusted[a] odds ratios for usual industry of employment in Texas female lung cancer study, 1976–1980

Industry category	Total number in category	Odds ratio	Confidence interval	χ^2
Agriculture	6	0.91	0.24, 3.53	0.02
Oil/gas extract	4	2.01	0.37, 10.84	0.66
Other mining	0	—	— —	—
Construction	2	4.95	0.75, 32.69	2.76
Chemical	2	3.93	0.40, 39.06	1.37
Petroleum	6	0.43	0.91, 2.00	1.16
Metals	2	3.93	0.40, 39.06	1.37
Shipbuilding	2	3.93	0.40, 39.06	1.37
Other manufacturing	23	2.70	0.95, 7.67	3.50
Transportation	12	0.78	0.22, 2.76	0.15
Services	74	1.26	0.75, 2.13	0.75
Professional/Governmental	93	1.08	0.69, 1.69	0.12
Sales	113	1.23	0.80, 1.90	0.92
Housewife	592	1.00	— —	—

[a]Adjusted for smoking (ever/never).

Table 16. Odds ratios for household member regularly employed in specific industry for Texas lung cancer study, 1976–1980: Males

Industry	Yes		Odds ratio	95% Confidence interval	χ^2
	Case	Control			
Asbestos manufacturing	6	2	2.60	0.60, 11.25	1.76
Cement manufacturing	5	5	0.99	0.30, 3.25	0.00
Insulation manufacturing	4	1	2.99	0.47, 19.04	1.48
Coal mining	11	4	2.57	0.86, 7.71	3.06
Shipyard/shipbuilding	58	52	1.11	0.75, 1.65	2.27
Demolition	5	3	1.54	0.40, 5.93	0.41
High-rise construction	11	9	1.19	0.50, 2.84	0.16

Table 17. Odds ratios for household member regularly employed in specific industry for Texas lung cancer study, 1976–1980: Females

Industry	Yes		Odds ratio	95% Confidence interval	χ^2
	Case	Control			
Asbestos manufacturing	5	10	0.55	0.20, 1.50	1.29
Cement manufacturing	5	10	1.17	0.32, 4.25	0.21
Insulation manufacturing	9	4	2.24	0.73, 6.94	2.07
Coal mining	7	12	0.63	0.25, 1.57	1.00
Shipyard/shipbuilding	99	102	1.02	0.75, 1.39	0.02
Demolition	5	7	0.77	0.25, 2.33	0.02
High-rise construction	37	26	1.52	0.91, 2.55	2.60

In addition to these analyses specific questions were asked regarding whether anyone in the household ever worked in the following industries: asbestos, cement, or insulation manufacturing; coal mining; shipyards and shipbuilding; demolition;

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high-rise construction. For both males and females a large number of cases and controls reported having a household member employed in a shipyard or in shipbuilding, but this was not associated with an increased odds ratio (1.11 for males and 1.02 for females) (Tables 16 and 17). Among males there were no statistically significant increases; however, the odds ratios for asbestos manufacturing, insulation manufacturing, and coal mining are increased. Similarly, for females the odds ratio is increased for insulation manufacturing and high-rise construction but not significantly.

Discussion

The availability of fairly large numbers of male and female incident lung cancer cases and comparison subjects in an interview study with detailed occupational histories provides an important basis for examining the contribution of occupational exposures to lung cancer in males and females. Recognizing the strong increase in lung cancer risk associated with cigarette smoking, such analyses need to control for smoking differences. Our preliminary analysis of usual occupation and industry of employment with a broad smoking adjustment (ever/never) indicates several occupational and industrial associations that need to be pursued in future analyses. Specifically, odds ratios are significantly increased for usual employment in several industries (construction, chemical, metal, and transportation) for males and the clerical occupations for females. In addition, there are several associations suggested by increased odds ratios, which are not statistically significant. For males, an increased risk is suggested for occupations in the structural category and employment in industries related to oil and gas extraction (SIC 13), petroleum refining (SIC 60–69), and shipbuilding (SIC 373). For females, occupations in the service category and industries in the other manufacturing group are associated with fairly stable increased odds ratios.

Future analysis of these data will examine the possible interaction of smoking with occupational and industrial groups and a possible need to employ more specific smoking strata. Examination of odds ratios for smoking strata within occupational and industrial categories suggested that an ever/never smoking classification would be sufficient to control for the confounding effect of smoking in the examination of overall risks associated with usual employment in specific occupational and industrial categories as presented here. However, this broad classification may not be sufficiently specific for an examination of interaction of smoking with workplace exposures. In these analyses the classification of "exposed" within a specific category is based upon the "usual" occupation or industry of employment rather than "ever employed" in a given work environment. The use of the usual pattern may be more conservative in the detection of occupational and industrial associations and is perhaps the more appropriate designation to use for a preliminary examination of the data. As noted, the use of the usual occupation and industry of employment did introduce some special constraints on the analysis of the female patterns in that the usual occupation and industry for over

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60% of the cases and controls was "Housewife." We will employ a number of more specific designations of occupational and industrial variables in future analyses.

Even with these recognized limitations, the suggestion which clearly emerges from our data is that there may be a wider variety of workplace exposures associated with substantial increments in the risk of lung cancer than currently recognized. In addition, use of the full work history, including dates will surely aid in refining the preliminary associations reported here.

The relationship of lung cancer cell type with age at time of diagnosis warrants further scrutiny in that the highest odds ratios for the smoking variables were observed for the youngest age group (< 57 years at time of diagnosis). The lack of a "passive smoking" effect when the confounding effect of smoking of individual study subjects is considered, is not consistent with early reports. Although subsequent reports are also not consistent with regard to this association, it may be that the study population available was not sufficiently large to detect a fairly low level effect and that this association needs to be assessed in a considerably larger study population.

These preliminary analyses demonstrate a strong and consistent smoking effect in males and females for all types of lung cancer. The risk differentials associated with cigarette smoking observed for adenocarcinoma and other lung cancer cell types are striking and consistent with findings of others (11). In addition, they reemphasize earlier suggestions that perhaps specific environmental exposures are more strongly associated with specific types of lung cancer. In addition, these data suggest that perhaps lung cancer is more similar in males and females than previously regarded and that the observed differentials in risk by sex are principally due to exposure differentials.

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Lung Cancer:

Causes and Prevention

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CHAPTER **14**

Lung Cancer in Japan: Effects of Nutrition and Passive Smoking

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ABSTRACT

Lung cancer is on a sharp increase in both men and women in Japan. Nonsmoking wives with smoking husbands were found to carry an elevated risk of lung cancer and ischemic heart disease by a large-scale cohort study, 1966-1981, for 265,118 adults in 29 Health Center Districts in Japan, the risk steadily going up with the increase in number of cigarettes smoked by the husband. In major cancers other than lung, no such risk elevation was observed. A nonsmoking husband with a smoking wife also showed an elevated risk of lung cancer. The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking just as for active smoking. Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking. Such risk reduction was not observed for ischemic heart disease. The observed results suggest that the influence of husband's smoking on nonsmoking wives in raising the risk of lung cancer is as a cancer promoter rather than a cancer initiator. This promoter hypothesis may explain why such continuous but low dose exposure of passive smoking, which starts after adult age is reached, significantly elevates lung cancer risk in nonsmoking wives.

Key Words: Japan, cohort study, passive smoking, lung cancer, ischemic heart disease, **green-yellow vegetables, β-carotene, promoter, promoter-inhibitor**

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Introduction

The mortality from lung cancer has been increasing rapidly in Japan (Figure 1). The number of deaths among males was 520 in 1947 and 17,555 in 1982, the corresponding number for females was 248 and 6661.

There exists little sign of a slowing down of the rate of increase, and the number of deaths from lung cancer are expected to exceed the number of deaths from stomach cancer in the near future. In parallel to this trend the number of cigarettes sold in Japan also has been on a sharp rise (Figure 1). The random sample survey conducted by the Tobacco Monopoly Corporation in 1982 revealed that currently 70.1% of adult males and 15.4% of adult females smoke in Japan.

The purpose of this chapter is to study the causative factors of lung cancer in Japan with special reference to the effect of passive smoking relative to the effect of active smoking. The possible influence of nutrition, β-carotene-rich green-yellow vegetables in particular, on the risk enhancing effect of active and passive smoking also is studied.

Methods

The materials of our ongoing large-scale cohort study for 265,118 adults aged 40 years and above in Japan were analyzed in detail to discover factors altering the

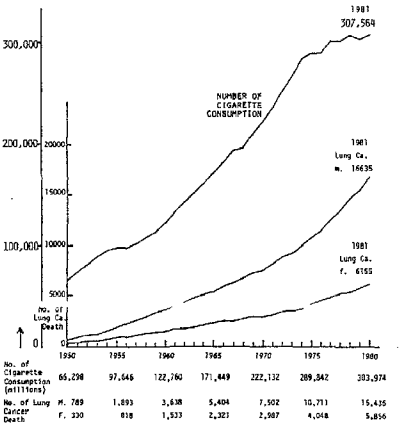

Figure 1. Trends in cigarette consumption and lung cancer deaths in Japan (1950–1981).

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risk of lung cancer in both men and women. For statistical analysis, programs included in the book *Epidemiologic Analysis with a Programmable Calculator* (U.S. Department of Health, Education and Welfare, 1979) mainly were used.

Results

Active Smoking and Lung Cancer Risk

Cigarette smoking was identified by far the most important cause of lung cancer in Japan, both by case-control studies conducted by the author and other researchers and by a large-scale cohort study (1–6) being conducted by the author for 265,118 adults (122,261 men and 142,857 women) aged 40 and above (95% of census population) in 29 Health Center Districts in Japan. These subjects were surveyed in October–December 1965 and followed up from January 1966 until December 1981. A clear-cut dose–response relationship was observed between the number of cigarettes ever smoked and the age-standardized mortality rate of lung cancer. The mortality rate of lung cancer also was found to be higher the earlier smoking was begun when age and total number of cigarettes ever smoked were standardized (Figure 2). The lung cancer-standardized mortality rate was observed

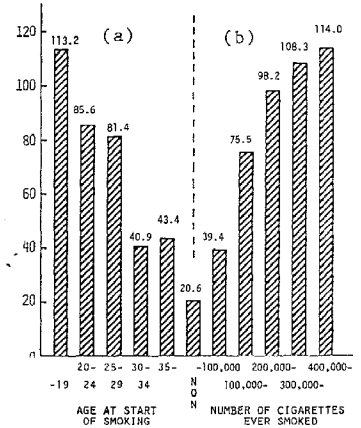

Figure 2. Lung Cancer. (a) Attained age- and amount of smoking-standardized mortality rate by age at start of smoking. (b) Attained age- and age at start of smoking-standardized mortality rate by total amount of cigarettes ever smoked. (Prospective study, 1966–1978 Japan.)

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to be 18.3% lower in smokers who do not inhale compared to regular deep inhalers, and 48.9% lower in smokers of filtertip cigarettes compared to smokers of nonfiltertip cigarettes, according to our cohort study. The risk of lung cancer in daily smokers also was noted to approach gradually that of nonsmokers with the lapse of years after smoking cessation, risk difference diminishing by 41.6% in 5 years after stopping the habit. This strongly suggests the major part of the influence of smoking during adulthood is the promoter action of substances included in mainstream smoke.

Effect of Nutrition on Active Smokers

Daily intake of green-yellow vegetables, rich in β-carotene, was found significantly to lower the risk of lung cancer (7, 8), particularly when the total amount of cigarettes ever smoked was less than 300,000 (6) (Figure 3). No other dietary habit showed such risk reduction. Risk reduction after smoking cessation appeared to be more pronounced in case of daily consumers of green-yellow vegetables. Taking similar evidence in laboratory studies into consideration, a promoter-inhibitor interaction model was conceptualized.

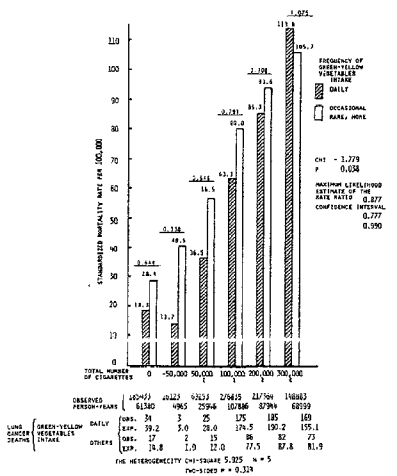

Figure 3. Standardized mortality rate for lung cancer by total number of cigarettes ever smoked and by frequency of green-yellow vegetable intake; males. (Prospective study, 1966-1978.)

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Passive Smoking and Lung Cancer

In the present cohort study (1966–1981), 427 deaths from lung cancer in women were recorded during 16 years of followup (1966–1981). Of these women, 269 were married, and 200 of these also were nonsmokers. These cases occurred among 91,540 nonsmoking married women whose husbands' smoking habits were studied. The risk of lung cancer was carefully measured, taking into consideration possible confounding variables. There was a statistically significant increased risk in relation to the extent of the husband's smoking (Figure 4), which confirmed the validity of previous reports (9, 10). The association was significant when observed by age of husbands (Table 1, Figures 1 and 5) and also by age of wives (Table 2). The further detailed analysis on materials cross-tabulated by age and occupation of the husband also confirmed the association (Table 3). The husband's drinking habits were noted to have no effect in raising the risk of lung cancer in nonsmoking wives (Table 4).

Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking also was observed with ischemic heart disease when observed by husband's age and occupation (Tables 5 and 6). The significant risk elevation of cancer of the nasal sinus also was observed in nonsmoking wives with husband's smoking. The risk elevation of emphysema and chronic bronchitis with spouse's smoking also was noted with borderline significance. However there was no tendency of risk elevation at all in major cancers other than lung (total of cancers of stomach, cervix, and breast), the standardized mortality rate in nonsmoking wives being almost exactly the same regardless of the husband's smoking habit (Table 7, Figure 6).

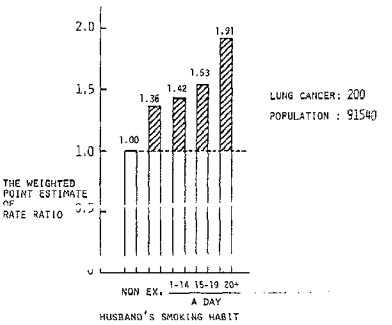

Figure 4. Age-standardized mortality rate ratio for lung cancer in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Table 1. Mortality rate for lung cancer in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966–1981, Japan[a]

	Husband's smoking habit									
					Number of cigarettes a day					
	Nonsmoker		Ex-smoker		1-14/d		15-19/d		20+/d		Total	
Husband's age group	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	4	6,229	1	1,255	8	8,621	6	5,158	16	10,764	35	32,027
50–59	10	7,791	3	1,922	20	9,668	8	4,052	24	9,820	65	33,253
60–69	18	7,120	11	2,687	28	7,243	9	2,513	23	4,651	89	24,214
70–79	5	755	2	348	2	612	1	105	1	226	11	2,046
Total	37	21,895	17	6,212	58	26,144	24	11,828	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.36	2.18 0.85	1.42	2.01 1.01	1.58	2.38 0.98	1.91	2.71 1.34	Mantel extension χ^2 2.915 one-tail p value 0.00178	
						1.45		2.02 1.04				
Mantel-Haenszel χ^2 one-tail p value	—			1.0855 0.1389		1.8290 0.0337				3.0295 0.0012		

Table 2. Mortality rate for lung cancer in nonsmoking wives by smoking habit of husbands and by age group of wife: prospective study: 1966-1981, Japan[a]

	Husband's smoking habit						
			Number of cigarettes a day				
	Nonsmoker		Ex-smoker 1-19/d		20+/d		Total	
Wife's age group	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	4	7,918	21	17,492	21	12,615	46	38,025
50–59	14	7,695	46	15,640	31	8,814	91	32,089
60–69	16	6,170	31	10,381	10	3,793	57	20,344
70–79	3	172	1	671	2	239	6	1,082
Total	37	21,895	99	44,184	64	25,461	200	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.43	2.01 0.99	1.74	2.55 1.19	Mantel extension χ^2 2.424 one-tail p value 0.00768	
Mantel-Haenszel χ^2 one-tail p value	—			1.6042 0.0543		2.3731 0.0088		

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Table 3. Mortality rate for lung cancer in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)[a]

Husbands age (year)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	4	6,229	15	15,034	16	10,764
	1		324		653	1	566
	2		90		231		293
	3	1	908	2	2,247	3	1,867
	4	1	476	1	993		1,044
	5	1	2,502	6	5,941	9	3,636
	6		46		165		108
	7		177	1	486	1	426
	8		1,112	3	3,431	2	2,241
	9		162	1	345		243
	10	1	432	1	542		340
50–59	Total	10	7,791	31	15,642	24	9,820
	1	1	345		593	2	446
	2		175		253	1	319
	3	1	817	5	1,764	1	1,324
	4	1	653	2	1,133	5	1,092
	5	4	3,497	16	6,812	9	3,514
	6		35		89		50
	7		120		273	1	234
	8	3	1,375	6	3,478	2	2,155
	9		164		378	1	251
	10		610	2	869	2	435
60–69	Total	18	7,120	48	12,443	23	4,651
	1		227	1	327	1	179
	2	1	91		143		124
	3		305	2	594	2	327
	4	2	508	5	822	1	500
	5	13	4,084	33	6,845	10	2,152
	6		9		31		14
	7		45		82		55
	8	1	805	5	1,784	4	736
	9		121	1	208		92
	10	1	925	1	1,607	5	472
70 +	Total	5	755	5	1,065	1	226
	1		32		30		5
	2		21		14		4
	3		18	1	36		8
	4		48		73		20
	5	3	323	1	446		89
	6		1		1		0
	7		1		5		1
	8		87	2	119	1	36
	9		11		19		2
	10	2	213	1	322		61
[a] Standardized Risk Ratios		1.000		1.436		1.872	

Mantel extension χ^2: 3.124; one-tail p value: 0.00089.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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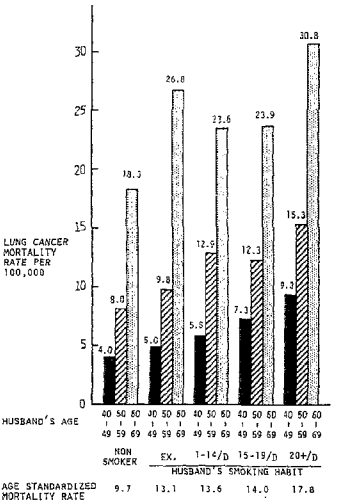

Figure 5. Age-specific mortality rate for lung cancer per 100,000 in nonsmoking wives by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

Table 4. Mortality rate for lung cancer in women by age group and by alcohol drinking habits of husband: (patient herself a nonsmoker): prospective study, 1966–1981, Japan

	Husband's drinking habits									
	Nondrinker		Occas. Rare		Daily		Obscure		Total	
Husband's age group	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	12	6,141	10	15,877	13	9,935	0	74	35	32,027
50–59	12	7,437	29	14,000	24	10,700	0	221	65	32,358
60–69	23	6,741	35	9,234	27	7,606	4	633	89	24,214
70–79	1	686	5	666	4	589	1	105	11	2,046
Total	48	21,005	79	40,443	68	28,910	5	1,170	200	91,510
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.03	1.61 0.66	1.11	1.59 0.77				
Mantel-Haenszel χ^2 one-tail p value	—			0.1019 0.4594		0.4564 0.3240			Mantel extension χ^2 0.626 one-tail p value 0.26566	

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Table 5. Mortality rate for ischemic heart diseases in women by age group and by smoking habits of husband: prospective study, 1966–1981, Japan

Husband's age group	Husband's smoking habit: Nonsmoker No.	Nonsmoker Pop.	Ex-smoker 1-19/d No.	Ex-smoker 1-19/d Pop.	20+/d No.	20+/d Pop.	Total No.	Total Pop.
40–49	13	6,229	40	15,034	33	10,764	86	32,027
50–59	26	7,791	56	15,642	49	9,820	131	33,253
60–69	65	7,120	125	12,443.	47	4,651	237	24,214
70–79	14	755	19	1,065	7	226	40	2,046
Total	118	21,895	240	44,184	136	25,461	494	91,540
The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.10 0.91	1.33	1.31 1.06	1.63	—	
Mantel-Haenszel χ^2 one-tail p value	—		0.8504 0.1976		2.0723 0.0191		Mantel extension χ^2 2.073 one-tail p value 0.01909	

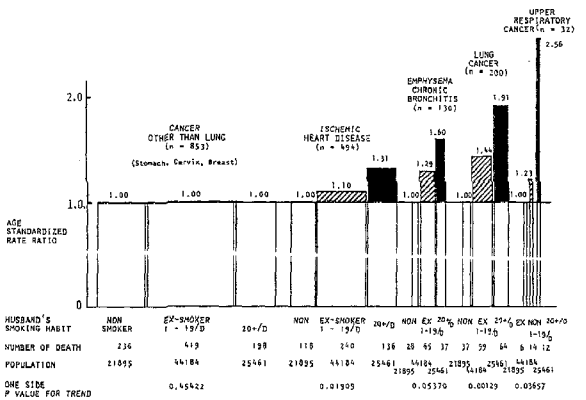

Figure 6. Standardized mortality rate ratio for selected causes of death in 91,540 nonsmoking women by smoking habits of their husbands. (Prospective study, 1966–1981, Japan.)

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Table 6. *Mortality rate for ischemic heart disease in women by age, occupation, and smoking habit of husbands (patient herself a nonsmoker)*[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	13	6,229	40	15,034	33	10,764
	1	1	324		653	1	566
	2		90	1	231		293
	3		908	4	2,247	1	1,867
	4		476	1	993	5	1,044
	5	8	2,502	25	5,941	18	3,636
	6		46		165		108
	7	1	177	2	486		426
	8		1,112	7	3,431	6	2,241
	9		162		345	1	243
	10	3	432		542	1	340
50–59	Total	26	7,791	56	15,642	49	9,820
	1	1	345	3	593		446
	2	2	175		253		319
	3	2	817	5	1,764	6	1,324
	4		653	6	1,133	4	1,092
	5	15	3,497	27	6,812	26	3,514
	6		35	1	89		50
	7		120	1	273	2	234
	8	5	1,375	8	3,478	11	2,155
	9		164	1	378		251
	10	1	610	4	869		435
60–69	Total	65	7,120	125	12,443	47	4,651
	1	2	277	2	327	1	179
	2	1	91	2	143	1	124
	3	2	305	5	594	1	327
	4	10	508	8	822	5	500
	5	36	4,084	79	6,845	27	2,152
	6		9	1	31		14
	7	1	45	1	82	1	55
	8	7	805	13	1,784	6	736
	9	1	121	2	208		92
	10	5	925	12	1,607	5	472
70+	Total	14	755	19	1,065	7	226
	1	2	32	1	30		5
	2	2	21		14	1	4
	3		18	1	36		8
	4	1	48	1	73		20
	5	5	323	11	446	2	89
	6		1		1		0
	7		1		3		1
	8		87	1	119	3	36
	9		11	2	19		2
	10	4	213	2	322	1	61
[a]Standardized Risk Ratios		1.000		1.103		1.359	

Mantel extension χ^2: 2.351; one-tail p value: 0.00936.

[b]Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

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Table 7a. Mortality rates for major cancers other than lung in women by age group and by smoking habit of husband (patient herself a nonsmoker): prospective study, 1966–1981, Japan[a]

Husband's age group	Husband's smoking habit (cigarettes a day)							
	Nonsmoker		Ex-smoker 1–19		20+		Total	
	No.	Pop.	No.	Pop.	No.	Pop.	No.	Pop.
40–49	44	6,229	117	15,034	71	10,764	232	32,027
50–59	97	7,791	191	15,642	119	9,820	407	33,253
60–69	160	7,120	274	12,443	106	4,651	540	24,214
70–79	14	755	20	1,065	8	226	42	2,046
Total	315	21,895	602	44,184	304	25,461	1,221	91,540
[a]The weighted point estimate of rate ratio and test-based 90% confidence limits	1.00		1.00	1.11 0.90	1.00	1.05 0.95		
Mantel-Haenszel χ^2 one-tail p value	—			−0.0015 0.4994		0.0449 0.4821	Mantel extension χ^2 0.115 one-tail p value 0.4542	

Table 7 b. Mortality rates for major cancers other than lung in women by age, occupation, and smoking habit of the husband (patient herself a nonsmoker)[a]

Husbands age (years)	Occupation[b]	Nonsmoker		Ex-smoker or 1–19/day		≥20/day	
		No.	Pop.	No.	Pop.	No.	Pop.
40–49	Total	45	6,229	120	15,034	74	10,764
	1	2	324	1	653	3	566
	2		90	1	231	2	293
	3	9	908	17	2,247	12	1,867
	4	3	476	8	993	8	1,044
	5	17	2,502	59	5,941	35	3,636
	6		46		165		108
	7	1	177	6	486		426
	8	10	1,112	21	3,431	13	2,241
	9	1	162	4	345	1	243
	10	2	432	3	542		340
50–59	Total	98	7,791	195	15,642	122	9,820
	1	13	345	2	593	3	446
	2	2	175	1	253	1	319
	3	14	817	16	1,764	10	1,324
	4	1	653	18	1,133	9	1,092
	5	49	3,497	81	6,812	56	3,514
	6		35		89		50
	7	2	120	4	273	2	234
	8	12	1,375	49	3,478	31	2,155
	9		164	7	378	4	251
	10	5	610	17	869	6	435
60–69	Total	161	7,120	227	12,443	106	4,651
	1	5	227	5	327	2	179
	2	5	91	3	143	3	124
	3	7	305	11	594	5	327
	4	5	508	28	822	12	500
	5	102	4,084	158	6,845	58	2,152

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Table 7 b. (cont.)

Husbands age (years)	Occupation[b]	Nonsmoker No.	Nonsmoker Pop.	Ex-smoker or 1–19/day No.	Ex-smoker or 1–19/day Pop.	≥20/day No.	≥20/day Pop.
	6		9	1	31		14
	7	1	45	3	82	2	55
	8	10	805	40	1,784	17	736
	9	2	121	3	208		92
	10	24	925	25	1,607	7	472
70 +	Total	14	755	21	1,065	8	226
	1		32		30		5
	2	1	21		14		4
	3	1	18		36		8
	4		48	1	73	2	20
	5	7	323	15	446	4	89
	6		1		1		0
	7		1		5		1
	8	1	87	2	119	1	36
	9		11		19		2
	10	4	213	3	322	1	61
[a] Standardized Risk Ratios		1.000		0.969		1.034	

Mantel extension χ^2: −0.129; one-tail p value: 0.44868.

[b] Occupation: 1, Professional and technical workers; 2, managers and officials; 3, clerical and related workers; 4, sales workers; 5, farmers, lumbermen, and fishermen; 6, workers in mining and quarrying occupations; 7, workers in transport and communication occupations; 8, craftsmen, production process workers, and laborers; 9, service workers; 10, not classifiable and not reported.

Comparison of the Effects of Active Smoking and Passive Smoking

When the risk of lung cancer in nonsmokers with nonsmoking spouses was taken as a unit, a definite dose–response relationship was observed, the highest risk being in heavy active smokers, followed by mild active smokers, then heavy passive smokers, and then mild passive smokers (Figure 7). The risk gradient was similar both in men and in women (Figure 8). A significantly elevated risk of lung cancer also was noted for nonsmoking husbands with smoking wives.

Because the size of population exposed to passive smoking is quite large in the case of women, the effect of passive smoking because of the husband's smoking was estimated as 65% of that of active smoking. Our recent survey showed that 47.5% and 32.6% of Japanese adult women were being exposed to passive smoking at home and at the workplace, respectively (Figure 9). Therefore it must be a sound estimate that the total effect of passive smoking is approximately equivalent to that of active smoking in women. However, as a majority of adult men are still smokers, the total effect of passive smoking relative to active smoking must be on

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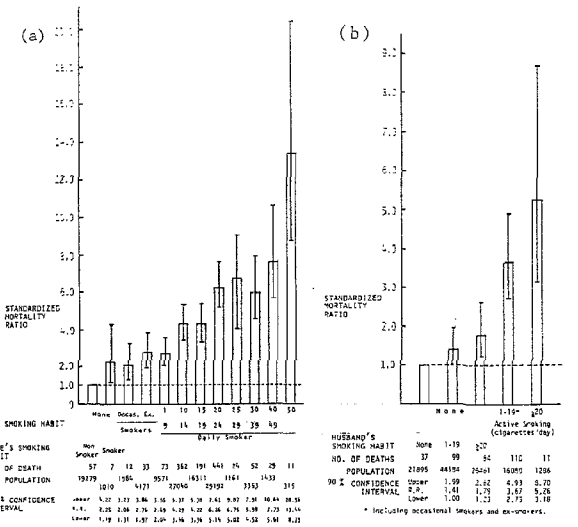

Figure 7. (a) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; males.(Prospective study, 1966–1981, Japan.) (b) Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals; females. (Prospective study, 1966–1981, Japan.)

the order of a few percent. The effect on lung cancer risk of passive smoking at home in relation to active smoking for men was calculated as 0.4% in our series.

Effect of Nutrition on Passive Smokers

A significantly lower risk of lung cancer was observed when nonsmoking wives with smoking husbands consumed green-yellow vegetables daily (Tables 8 and 9, Figures 10 and 11) suggesting that the promoter-inhibitor interaction model also applied to passive smoking just as in active smoking (Figure 9). Such risk reduction caused by daily intake of green-yellow vegetables was not observed for ischemic heart disease (Table 10, Figure 12).

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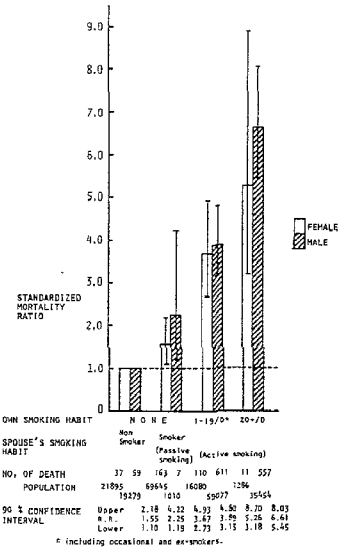

Figure 8. Active and passive smoking and lung cancer mortality: relative risks (RR) with 90% confidence intervals. (Prospective study, 1966–1981, Japan.)

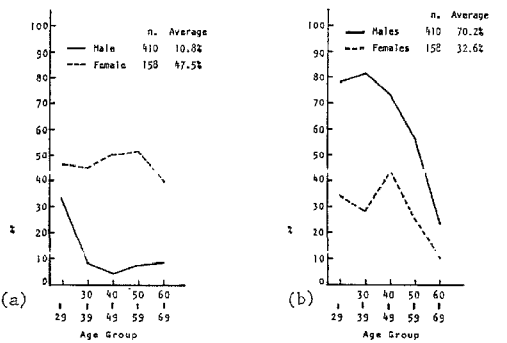

Figure 9. (a) Percentage of nonsmokers exposed to sidestream smoke at home, Japan, 1983. (b) Percentage of nonsmokers exposed to sidestream smoke at the workplace, Japan, 1983.

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Table 8. Lung cancer mortality rate in nonsmoking wives by smoking habit of the husband: comparison between daily and non daily intake of green-yellow vegetables

Husband's smoking habits		Nonsmoker				Ex-smoker on 1-19 day				≥ 20/day			
Wife's eating habits		Green-yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age												
Agriculture	40–49	1,958	1	544	0	5,050	5	891	1	3,037	7	599	2
	50–59	2,805	4	692	0	5,196	11	1,616	5	2,588	9	926	0
	60–69	3,359	7	725	6	5,106	22	1,739	11	1,588	6	564	4
	70–79	258	3	65	0	287	1	159	0	45	0	44	0
Others	40–49	2,422	3	1,305	0	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	3,181	5	1,113	1	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	2,266	4	770	1	4,088	9	1,510	6	1,906	10	593	3
	70–79	216	2	216	0	371	1	248	3	81	1	56	0
Total		16,465	29	5,430	8	34,118	69	10,066	30	19,255	43	6,206	21

Grand total: Population: 91540 — Lung cancer: 200

Green-yellow vegetables	Mantel-extension χ^2	P-value (two tailed)
Daily	2.072	0.03827
Nondaily	2.487	0.01288
Total	3.090	0.00200

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Table 9. Effect of daily intake of green-yellow vegetables on lung cancer mortality in nonsmoking wives with smoking husbands[a]

Husband's smoking habit		Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green-yellow vegetables							
		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.	Pop.	Lung Ca.
Occupation	Age								
Agriculture	40–49	5,050	5	891	1	3,037	7	559	2
	50–59	5,196	11	1,616	5	2,588	9	926	0
	60–69	5,106	22	1,739	11	1,588	6	564	4
	70–79	287	1	159	0	45	0	44	0
Others	40–49	7,288	8	1,805	1	5,377	5	1,751	2
	50–59	6,732	12	2,098	3	4,633	5	1,673	10
	60–69	4,088	9	1,510	6	1,906	10	593	3
	70–79	371	1	248	3	81	1	56	0
Total		34,118	69	10,066	30	19,255	43	6,206	21

[a]Mantel-Haenszel χ^2: −1,986; p (two-tailed 0.047). Odds ratio: Nondaily green-yellow vegetable intaker, 1,000; daily green-yellow vegetables intake, 0.707 (standardized rate ratio); 90% confidence limits, 0.538–0.943.

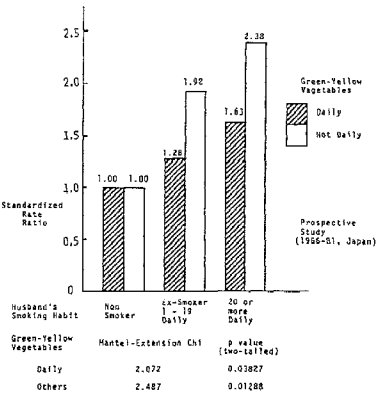

Figure 10. Lung cancer mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

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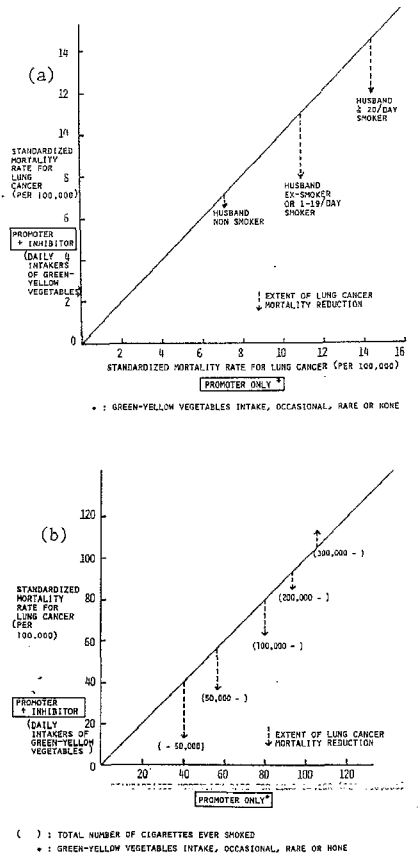
(a)
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER + INHIBITOR
(DAILY INTAKERS OF GREEN-YELLOW VEGETABLES)
HUSBAND NON SMOKER
HUSBAND EX-SMOKER OR 1-19/DAY SMOKER
HUSBAND ≥ 20/DAY SMOKER
EXTENT OF LUNG CANCER MORTALITY REDUCTION
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER ONLY *
* : GREEN-YELLOW VEGETABLES INTAKE, OCCASIONAL, RARE OR NONE
(b)
STANDARDIZED MORTALITY RATE FOR LUNG CANCER (PER 100,000)
PROMOTER + INHIBITOR
(DAILY INTAKERS OF GREEN-YELLOW VEGETABLES)
(300,000 -)
(200,000 -)
(100,000 -)
(50,000 -)
(- 50,000)
EXTENT OF LUNG CANCER MORTALITY REDUCTION
PROMOTER ONLY*
( ) : TOTAL NUMBER OF CIGARETTES EVER SMOKED
* : GREEN-YELLOW VEGETABLES INTAKE, OCCASIONAL, RARE OR NONE

Figure 11. (a) Standardized mortality rate for lung cancer in nonsmoking wives by smoking habit of the husband. Comparison between daily and nondaily intake of green-yellow vegetables. (Prospective study, 1966–1981, Japan.) (b) Standardized mortality rate for lung cancer according to total number of cigarettes smoked and frequency of consumption of green-yellow vegetables; males. (Prospective study, 1966–1978, Japan.)

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Table 10. Ischemic heart disease mortality rate in nonsmoking wives by smoking habit of the husband: comparison between green-yellow vegetables intake daily and nondaily

Husband's smoking habit		Nonsmoker				Ex-smoker or 1–19/day				≥ 20/day			
Wife's eating habit		Green–yellow vegetables											
		Daily		Nondaily		Daily		Nondaily		Daily		Nondaily	
Husband's		Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.	Pop.	Ischemic Heart D.
Occupation	Age												
Agriculture	40–49	1,958	6	544	2	5,050	18	891	7	3,037	14	599	4
	50–59	2,805	11	692	4	5,196	25	1,616	2	2,588	21	926	5
	60–69	3,359	30	725	6	5,106	55	1,739	24	1,588	21	564	6
	70–79	258	2	65	3	287	10	159	1	45	2	44	0
Others	40–49	2,422	3	1,305	2	7,288	10	1,805	5	5,377	12	1,751	3
	50–59	3,181	8	1,113	3	6,732	18	2,098	11	4,633	17	1,673	6
	60–69	2,266	21	770	8	4,088	33	1,510	13	1,906	11	593	9
	70–79	216	7	216	2	371	6	248	2	81	3	56	2
Total		16,465	88	5,430	30	34,118	175	10,066	65	19,255	101	6,206	35

Grand total	Population: 91540	Ischemic heart disease: 494

Green-yellow vegetables	Mantel-extension χ^2	P value (two tailed)
Daily	2.307	0.02105
Nondaily	0.820	0.41222
Total	2.406	0.01613

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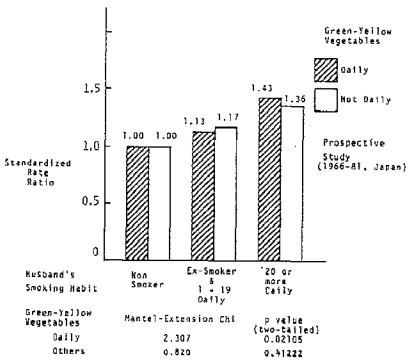

Figure 12. Ischemic heart disease mortality ratio in nonsmoking wives by smoking habits of their husbands. Comparison between daily and nondaily intake of green-yellow vegetables.

Discussion

The age-adjusted mortality rates for lung cancer have been sharply increasing both for men and for women in Japan. As only a fraction of Japanese women with lung cancer smoke cigarettes, the reasons for the trend of their mortality from lung cancer have been unclear. The present study appears to explain at least a part of this long-standing riddle.

This observation also questions the validity of the conventional method of assessing the relative risk of developing lung cancer in smokers by comparing them with nonsmokers. This study shows that nonsmokers are not a homogeneous group and should be subdivided according to the extent of previous exposure to indirect or passive smoking. Although the relative risk of indirect smoking was smaller than that of direct smoking, the absolute excess deaths from lung cancer resulting from passive smoking must be important because of the large size of the exposed group. Therefore, these results of our current study must be of public health importance, strengthening already existing evidence for a health hazard from passive smoking (11–13) (Table 11).

As shown in Figure 9, 47.5% and 32.6% of 158 nonsmoking adult women surveyed recently are noted to be exposed to sidestream smoke at home and at the workplace, respectively. One survey conducted in Aichi prefecture in Japan showed that nonsmoking wives are exposed to their husband's smoking 6.7 times a day on the average.

Because sidestream smoke contains varieties of cancer promoters at higher concentration than does mainstream smoke, it must be reasonable to consider the

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Table 11. Passive smoking is hazardous to health

1. Existence of toxic substances (including carcinogens) in sidestream smoke mostly at higher concentration than in mainstream smoke.
2. Existence of a large number of nonsmokers who have to inhale sidestream smoke frequently and intensively for long years at home and/or at the workplace.
3. Existence of sidestream smoke component in blood and urine of nonsmokers exposed to passive smoking, (eg, nicotine, CO-Hb in blood and Mutagens in urine).
4. Existence of functional abnormalities in nonsmokers exposed heavily to passive smoking (eg, respiratory or circulatory function).
5. Lung tissue damage and destruction in chronic passive smokers as shown by elevated hydroxyproline excretion in urine.
6. Higher incidence of selected diseases in nonsmokers exposed heavily to passive smoking (eg, pneumonia, bronchitis, asthma, ischemic heart disease, lung and nasal sinus cancer).
7. Experimental evidence.

main effect of passive smoking on lung cancer risk results from the prolonged exposure to such promoters in sidestream smoke. The risk-inhibitory effect of a daily intake of green-yellow vegetables that are rich in β-carotene must be considered as an additional evidence for such a promoter action hypothesis of passive smoking. The hypothesis also explains why exposure to passive smoking that starts after reaching adult age can significantly influence the risk of lung cancer.

The histology of 21 cases of lung cancer in nonsmoking wives of smoking husbands was not essentially different from that in smoking women (adenocarcinoma 57.1%, squamous cell carcinoma 19.0%, and small-cell carcinoma 4.8%). A case-control study conducted within our cohort study revealed a significant dose-response relationship between adenocarcinoma of the lung and the number of cigarettes smoked daily, relative risk being 1.39 and 5.75 for smokers of 1–14 and 15 or more cigarettes daily, the chi square for the trend being 6.848 with a one-tail p value of 0.004. Therefore the predominance of adenocarcinoma of the lung in nonsmoking women with smoking husbands should not be considered unfavorable evidence for promoter action hypothesis of passive smoking. In passive smoking, sidestream smoke usually is inhaled through the nose, whereas in active smoking mainstream smoke always is inhaled through the mouth. This difference could be a reason for the elevated risk of nasal sinus cancer in passive smokers. The mechanism of the action of passive smoking on the risk of ischemic heart disease, however, must be explained in different ways (eg, a combined action of carbon monoxide and nicotine).

In summary, to reduce the effect of active and passive smoking and to encourage the effect of nutrition, in particular β-carotene intake, would be the most productive source for lung cancer prevention. For selected persons exposed to other known carcinogens, eg, those related to occupation or radiation, such environmental exposure also must be minimized in addition to the preventive measures focused on lifestyle variables given above.

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Jahrgang 10
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Anlage und Umwelt bei Pneumologischen Krankheitsbildern

Teil I

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Atemw.-Lungenkrkh. Jahrgang 10, Nr. 11/1984, S. 606–609

Rauchen und Umweltfaktoren beim Bronchialkarzinom

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Rauchen und Umweltfaktoren beim Bronchialkarzinom. Wie bei keiner anderen Krebserkrankung sind beim Lungenkrebs die Ursachen für das Entstehen des Tumors bekannt. Es handelt sich in erster Linie um exogene Noxen, die grundsätzlich einer Intervention zugänglich sind. Als wichtigste Noxe konnte das Zigarettenrauchen identifiziert werden. Verantwortlich sind eine Reihe von Kanzerogenen und Kokanzerogenen im Rauchkondensat (Teer). Berufliche Noxen und andere Ursachen spielen vergleichsweise eine quantitativ untergeordnete Rolle. Es konnte keine wesentliche Bedeutung der allgemeinen Luftverschmutzung als Lungenkrebs-Ursache nachgewiesen werden. Bei bestimmten beruflichen Expositionen führt Zigarettenrauchen zu einem zusätzlichen Ansteigen des Lungenkrebsrisikos. Die berufliche Exposition ist der zweifellos wichtigste umweltbedingte Faktor. Wir stellen eine gewisse (geringe) Risikoerhöhung für Angehörige bestimmter Berufsgruppen fest, aber nur wenn zusätzlich eine Rauchkondensat-Belastung besteht. Es spricht alles dafür, daß das Risiko durch Passivrauchen, wenn tatsächlich vorhanden, auf einen »low dose-effect« zurückzuführen ist, der vernachlässigt werden kann, da er keinen wesentlichen Einfluß auf die Lungenkrebsinzidenz ausübt und damit in keinem Verhältnis zum Aktivrauchen steht. Eine Studie über Bronchuskarzinom bei Männern unter 40 Jahren zeigt, auch bei diesen seltenen Fällen, die überragende ätiologische Bedeutung des Rauchens.

Schlüsselwörter: Lungenkrebs – Rauchen – berufliches Krebsrisiko.

Smoking and occupational factors in lung cancer. The etiological role of tobacco consumption for the lung cancer epidemic is very well established. Occupational exposures may play a minor role in increasing lung cancer risk among heavy smokers. We refer to our own epidemiological studies and stress the fact that occupational exposure is the most important environmental factor in lung cancer epidemiology next to active smoking. Cigarette smoking is the most important factor by far, passive smoking most probably not substantially related to lung cancer risk. A study on lung cancer in men younger than 40 years demonstrated the importance of cigarette smoking, even in this relatively young patients.

Key words: Lung cancer – smoking – occupational exposures.

Einleitung

Die Beziehung zwischen Tabakkonsum und Bronchialkarzinom ist die vermutlich bestuntersuchte auf dem Gebiete der Epidemiologie der bösartigen Tumoren. Dennoch sieht sich der Sozialmediziner immer wieder veranlaßt, die ätiologische Bedeutung des Rauchens betonen zu müssen. Vor allem gilt dies im Zusammenhang mit der Beeinflussung der öffentlichen Meinung. Repräsentative Umfragen haben zum Beispiel in Österreich ergeben, daß die Luftverschmutzung als wesentlicher Faktor für die Entstehung des Lungenkrebses angesehen wird [2, 4], eine Meinung, die mit den wissenschaftlichen Erkenntnissen nicht übereinstimmt.

In dieser Arbeit sollen vor allem eigene Ergebnisse referiert werden, die sich aus einer langjährigen intensiven epidemiologischen Arbeit ergeben haben. Dabei kamen auch neue Erhebungsverfahren zum Einsatz, die eine genauere Anamnese der Dynamik des Rauchverhaltens von Patienten und Kontrollpersonen ermöglichen und damit auch eine bessere quantitative Risikobeurteilung.

Wir nehmen vor allem auf folgende Aspekte des Problems Rauchen und Umweltfaktoren beim Bronchialkarzinom Bezug:

– Bronchuskarzinom und berufliche Exposition, die der zweifellos wichtigste umweltbedingte Faktor ist.

– Lungenkrebs-Risiko und Passivrauchen, ein zur Zeit überaus aktuelles Thema.

– Bronchuskarzinom bei Männern unter 40 Jahren, um auch bei diesen seltenen Fällen die überragende ätiologische Bedeutung des Rauchens zu zeigen.

Einige Schlußfolgerungen sollen schließlich auf die Notwendigkeit und Möglichkeit zur Intervention gegen das Bronchialkarzinom hinweisen.

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	n	% Raucher	% Kreyberg I
Gummi-, Farbstoff-, Chemikalienerzeugung und -verarbeitung	82	96	88
Textilverarbeitung	21	90	90
Holzverarbeitung	55	96	95
Steingewinnung und -verarbeitung	177	99	93
Kohlenstaub	32	100	100
Metallgewinnung und -verarbeitung	197	97	87
Chauffeur	93	98	98
Land- und Forstwirtschaft	75	91	89
»white collar«	252	98	86
Kontrollpersonen: Berufe zusammen	828	75	

Tab. 1 Männliche Bronchuskarzinompatienten (ausgewählte Berufsgruppen) und Kontrollpersonen, Rauchstatus und Anteil Kreyberg I-Patienten.

	Jahre geraucht		Teer-Expositionswert	
Gummi-, Farbstoff-, Chemikalienerzeugung und -verarbeitung	41,6	(1,0)	2437	(219)
Textilverarbeitung	40,8	(2,4)	2156	(206)
Holzverarbeitung	40,7	(1,4)	2447	(161)
Steingewinnung und -verarbeitung	40,9	(0,8)	2544	(103)
Kohlenstaub	44,4	(1,4)	2774	(245)
Metallgewinnung und -verarbeitung	41,6	(0,8)	2418	(93)
Chauffeur	41,6	(1,1)	2569	(145)
Land- und Forstwirtschaft	43,1	(1,2)	2390	(162)
»white collar«	42,3	(0,7)	2649	(105)
Kontrollpersonen: Berufe zusammen	36,4	(0,8)	2026	(97)

Tab. 2 Männliche Bronchuskarzinompatienten (ausgewählte Berufsgruppen) und Kontrollpersonen, durchschnittliche Rauchdauer in Jahren, durchschnittlicher Teer-Expositionswert (1 SF).

Bronchuskarzinom und berufliche Exposition

Von allen Umwelteinflüssen, die im Zusammenhang mit dem Lungenkrebs-Risiko diskutiert werden, kommt der beruflichen Exposition die größte Bedeutung zu.

Folgende berufliche Noxen werden in der Literatur erwähnt: Asbest, Arsen, Nickel, Chrom, ionisierende Strahlen, Generatorgas, Vinylchlorid, Beryllium, Kadmium. Außerdem wurden die Staubarbeiter als Risikogruppe definiert.

Wir haben in umfangreichen Fall-Kontroll-Studien zur Bearbeitung der Fragestellung »Bronchuskarzinom und berufliche Exposition« beigetragen.

In einer überregional durchgeführten Erhebung [7] wurden Daten von 1583 männlichen Bronchuskarzinompatienten und 3160 Kontrollpersonen erhoben. Das große Datenmaterial ermöglichte Analysen nach Berufsgruppen. Für Raucher wurde das berufsbedingte Risiko bei Angehörigen der Berufsgruppen »Metallgewinnung und -verarbeitung« = »Metall« [9], »Chauffeur« [10], »Gummi-, Farbstoff-, Chemikalienerzeugung und -bearbeitung« = »Chemie« [11] und »Steinabbau und -verarbeitung« = »Stein« [8] ermittelt.

Als Vergleichskollektiv dienten Raucher, bei denen anamnestisch eine berufliche Exposition (Inhalationsnoxen) ausgeschlossen werden konnte (= »white collar« = Büroberufe). Um die Beeinflussung durch unterschiedliche Rauchgewohnheiten zu eliminieren, erfolgte die Adjustierung der Rauchgewohnheit nach Teer-Expositionswert (= TEW); dies ist eine Maßzahl, die Menge, Konsumdauer und Schadstoffgehalt aller jemals gerauchten Zigaretten berücksichtigt.

In Tabelle 1 sind der Anteil der Raucher und Kreyberg I*-Patienten ausgewählter Berufsgruppen sowie der Anteil der Raucher einer Gruppe von Kontrollpersonen dargestellt.

Auf die dominierende Bedeutung des Zigarettenrauchens für das Entstehen von Lungenkrebs bei den Angehörigen dieser Berufsgruppen weist der hohe Anteil von Rauchern hin. Entsprechend dominieren die Tumoren der histologischen Typen der Gruppe Kreyberg I. Das extreme Rauchverhalten der Patienten, verglichen mit den Rauchern unter den Kontrollpersonen, zeigt sich noch deutlicher an der signifikant längeren Konsumgewohnheit sowie

* Kreybeg I (WHO-Klassifikation) = Plattenepithelkarzinom.

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Beruf	Jahre berufstätig <10	11–20	21–30	31–40	>41	insgesamt
Metallgewinnung und -verarbeitung	1,4	1,9*	1,7**	1,2	1,6	1,5
Gummi-, Farbstoff-, Chemikalienerzeugung und -verarbeitung	1,6*	2,7*	1,1	1,4	1,0	1,3
Chauffeur	0,4	1,4	1,7	1,2	2,9	1,5**
Steinabbau und -verarbeitung	2,2*	2,7*	2,6*	1,6	1,8	2,0*

* $p > 1\%$, ** $p < 5\%$

Tab. 3 Lungenkrebsrisiko von Zigarettenrauchern ausgewählter Berufsgruppen gegenüber Zigarettenrauchern ohne berufliche Exposition („white collar" R = 1,0) nach Dauer der Berufstätigkeit.

an dem signifikant höheren Teer-Expositionswert (Tab. 2).

In Tabelle 3 ist das Lungenkrebsrisiko (adjustiert nach Alter und Teer-Expositionswert) von Zigarettenrauchern der Berufsgruppen „Metall", „Chauffeur", „Chemie" und „Stein" verglichen mit Zigarettenrauchern der Gruppe „white collar" dargestellt. Berufsexponierte Raucher weisen ein etwas höheres Erkrankungsrisiko als nicht exponierte Raucher auf.

Inwieweit Faktoren aus dem Berufsbereich hier kausal wirken oder die Wirkung des Tabakrauchens verstärken, kann aus diesen Untersuchungen nicht abgeschätzt werden. In der metallverarbeitenden und chemischen Industrie wurde eine Reihe von karzerogenen Noxen identifiziert. Die hier dargestellten Berufsgruppen »Metall« und »Chemie« sind zwar sehr weitgefaßt, es ist aber anzunehmen, daß das berufsbedingte Risiko durch einzelne Berufssparten bestimmt wird, in denen Noxen nicht nur verstärkend, sondern auch kausal gewirkt haben. Homogener in ihrer Zusammensetzung sind die Berufsgruppen »Chauffeur« und »Stein«. Chauffeure sind gegenüber polyzyklischen Kohlenwasserstoffverbindungen sowie Asbestfasern (Abrieb von Kupplungs- und Bremsbelägen) in höherem Ausmaß exponiert; kausale Beziehungen sind denkbar.

In der Berufsgruppe »Stein« kann eine kanzerogene Wirkung der unspezifischen Staubbelastung selbst, wie sie für das Untersuchungskollektiv angenommen werden kann, nicht als Ursache dieses berufsbedingten Risikos angenommen werden, vielmehr ein durch die Staubbelastung ausgelöster Prozeß, der die Wirkung des Tabakrauchens verstärkt.

Schlußbemerkung

Die dargestellten Ergebnisse zeigen die Bedeutung beruflicher Noxen für das Entstehen von Lungenkrebs auf. Wenn auch die Noxe Tabak ätiologisch wesentlich höher einzuschätzen ist, sollten berufliche Expositionen nicht vernachlässigt werden.

Durch Arbeitsschutzmaßnahmen und Veränderung industrieller Prozesse konnten vielfach berufliche Expositionen verhütet bzw. reduziert werden. Neue Arbeitsprozesse können jedoch neue Expositionen schaffen. Die Fahndung nach kanzerogenen Gefahren am Arbeitsplatz muß daher weiter intensiv durchgeführt werden.

Lungenkrebsrisiko und Passivrauchen

Im Jahr 1981 wurden drei Studien veröffentlicht, die sich mit der Fragestellung Passivrauchen und Lungenkrebs auseinandergesetzt haben. Es handelt sich dabei um jeweils eine Kohortenanalyse aus Japan [3] und den USA [1] sowie um eine Fall-Kontroll-Studie aus Griechenland [6]. In der japanischen und griechischen Untersuchung konnte ein signifikant erhöhtes Lungenkrebsrisiko bei passivrauchenden Frauen, einschließlich einer Dosis-Wirkung-Beziehung, nachgewiesen werden. Die amerikanische Untersuchung konnte bei passivrauchenden Frauen ein nur geringfügiges, nicht signifikant erhöhtes Lungenkrebsrisiko nachweisen; eine Dosis-Wirkungs-Beziehung bestand nicht.

In einer auf dosimetrischen Überlegungen beruhenden Analyse kommen wir [8] zu folgender Beurteilung:

Es spricht alles dafür, daß das Risiko durch Passivrauchen, wenn tatsächlich vorhanden, auf einen »low dose-effect« zurückzuführen ist, der vernachlässigt werden kann, da er keinen wesentlichen Einfluß auf die Lungenkrebsinzidenz ausübt und damit in keinem Verhältnis zum Aktivrauchen steht.

Wie auch die Diskussion bei der Fragestellung Luftverschmutzung und Lungenkrebs wird auch die Diskussion Passivrauchen und Lungenkrebs vor allem emotionell geführt und generell überbewertet. Dies führt leider dazu, daß vom noch immer ungelösten Problem, dem Aktivrauchen, abgelenkt wird.

Bronchuskarzinom bei Männern unter 40 Jahren

In einer Fall-Kontroll-Studie haben wir uns mit der Beziehung zwischen Bronchuskarzinom und

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Tabakrauchen bei relativ jungen Patienten (unter 40 Jahren) beschäftigt [12]. Mit einer einzigen Ausnahme waren alle 13 untersuchten Patienten Zigarettenraucher, die ihre Konsumgewohnheit nicht eingestellt haben und verglichen mit den Rauchern in der Kontrollgruppe ein extremes Rauchverhalten aufweisen. Insgesamt sind bei Männern unter 40 Jahren maximal Dreiviertel aller Karzinom-Fälle dem Zigarettenrauchen zuzuschreiben.

Aus sozialmedizinischer Sicht ist diese Altersgruppe von besonderem Interesse, da die Konsumgewohnheit der Raucher dieser Gruppe in einen Zeitraum fällt, in dem eine Abnahme des durchschnittlichen Schadstoffgehaltes der Zigaretten sowie ein Trend von den schadstoffreichen filterlosen Zigaretten zu den schadstoffärmeren Filterzigaretten festgestellt werden kann.

Schlußfolgerungen

Aufgrund des gegebenen Wissensstandes haben wir folgende Konsequenzen für die Intervention gegen das Bronchuskarzinom gezogen [4], die wir durch neuere Untersuchungen, auch aus dem eigenen Institut, bestätigt sehen:

– Wie bei keiner anderen Krebserkrankung sind beim Lungenkrebs die Ursachen für das Entstehen des Tumors bekannt. Es handelt sich in erster Linie um exogene Noxen, die grundsätzlich einer Intervention zugänglich sind.

– Als wichtigste Noxe konnte das Zigarettenrauchen identifiziert werden. Verantwortlich sind eine Reihe von Kanzerogenen und Kokanzerogenen im Rauchkondensat (Teer).

– Berufliche Noxen und andere Ursachen spielen vergleichsweise eine quantitativ untergeordnete Rolle. Es muß besonders festgehalten werden, daß keine wesentliche Bedeutung der allgemeinen Luftverschmutzung als Lungenkrebs-Ursache nachgewiesen werden konnte.

– Bei bestimmten beruflichen Expositionen führt Zigarettenrauchen zu einem zusätzlichen Ansteigen des Lungenkrebsrisikos.

Wir teilen die Ansicht von [13], daß es noch einige wichtige Forschungsanliegen auf dem Gebiet der Lungenkrebs-Epidemiologie gibt; dazu zählen unter anderem die weitere Beurteilung der Frage des möglichen Einflusses des Passivrauchens, die Auswirkungen der veränderten Rauchgewohnheiten der Bevölkerung sowie der Einfluß von Ernährungsfaktoren auf das Bronchuskarzinom-Risiko.

Es muß aber festgehalten werden, daß bereits die vorhandenen Informationen ausreichen, dringend notwendige gesundheitspolitische Maßnahmen einzuleiten bzw. fortzusetzen, welche die Grundlage jeder sinnvollen Intervention gegen das Bronchuskarzinom sein müssen.

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Lung Cancer and Use of Cigarettes: A French Case-Control Study [1,2]

Simone Benhamou,[3] Ellen Benhamou,[4] Margot Tirmarche,[5] *and* Robert Flamant[3,6]

ABSTRACT—A case-control study of 1,625 cases and 3,091 controls was conducted in France from 1976 to 1980 to compare the effects of different smoking habits, especially the use of filter cigarettes, tobacco types (light or dark), and the use of hand-rolled or manufactured cigarettes on the occurrence of lung cancer. All cases had histologically confirmed lung cancer; the controls were matched by sex, age, hospital of admission, and interviewer. The reported results concern only male nonsmokers and males who smoked (or had smoked) cigarettes exclusively, i.e., a total of 1,217 Kreyberg I and Kreyberg II cancer cases and 1,915 controls. Cigarette smoking was associated with both Kreyberg I and Kreyberg II cell categories although with different relative risks (RR) (17.2 and 3.6, resp.). Within the Kreyberg I category, RR were significantly increased ($P<.0001$) with certain indices of duration and intensity of cigarette exposure, such as early age at first cigarette smoked, daily consumption, depth of inhalation, and duration of smoking. A significant difference in risk was found within the Kreyberg I category for nonfilter versus filter cigarette smokers (RR=18.1 and 10.9, resp.) and dark versus light tobacco smokers (RR=18.1 and 4.9, resp.) but not for hand-rolled versus manufactured cigarette smokers (RR=19.8 and 16.0, resp.). When all the covariates were taken into account in a matched logistic regression, lung cancer risks for nonfilter versus filter cigarette smokers was RR=1.23, for hand-rolled versus manufactured cigarette users RR=1.22, and for dark versus light tobacco users RR=1.94.—JNCI 1985; 74:1169-1175.

At present, lung cancer is the most important cause of cancer death among men in many industrialized countries, including France (*1*). Over the past 30 years, the association between lung cancer and tobacco (principally cigarette consumption) has been demonstrated in a large number of epidemiologic studies (*2-17*). Several characteristics of smoking habits have been studied, including (for cigarettes) the type of tobacco and the use of filters. Filter cigarettes were first introduced in England and in the United States during World War II, but did not dominate the market until the 1960's. In France, their introduction dates back only about 30 years, and they still represent only a minority of sales. Most studies have shown a lower risk of lung cancer among smokers of filter cigarettes than among smokers of nonfilter cigarettes (*7, 13-18*). With regard to the type of tobacco (light or dark), the situation in France is different from that in England and the United States, since cigarettes made of dark tobacco represented about 82% of the total sales in 1976 (*19*), whereas in England and in the United States, cigarettes are almost exclusively made with light tobaccos. We report here the results of a case-control study which ... the role of different smoking habits in the ... of lung cancer. Among the various measures of exposure to tobacco, the use of filter cigarettes, the type of tobacco (light or dark), and the use of hand-rolled or manufactured cigarettes have been studied especially.

METHODS

Subjects.—An epidemiologic study of lung cancer was conducted simultaneously in France and in four other European countries [Austria, Germany, Italy (Milan, Rome), and Scotland] with the support of the U.S. National Cancer Institute. In France, this case-control study was performed from 1976 to 1980 in 16 French hospitals, 13 of which are located in Paris. A total of 1,625 cases and 3,091 controls were included. The reported results concern males who had never smoked anything but cigarettes, as well as nonsmokers, i.e., 1,334 (87.2%) cases and 2,409 (81.3%) controls, respectively, of the whole study population.

Lung cancer patients were interviewed by 9 interviewers, either during hospitalization or during consultation for endoscopy; all lung cancer cases had to be histologically confirmed, and all had been diagnosed less than 1 year before the interview. Cases assessed only on clinical grounds were not included. All hospitalized cases were visited, except during periods of absence of the inter-

Abbreviations used: CI=confidence interval(s); RR=relative risk(s).

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viewer. Diagnoses were ascertained by admission records and, if necessary, with the help of hospital staff. Patients were classified into 6 possible histologic categories: The first 3 constitute the Kreyberg I category (squamous cell, small spindle oat cell, and "Kreyberg I type cell not distinguished"); the fourth (adenocarcinoma type) constitutes the Kreyberg II category; and the final 2 categories were "mixed Kreyberg I and II," and "Kreyberg type not distinguished." Of the 1,334 cases, 952 were of squamous type (71.3%), 146 of undifferentiated type (10.9%), 119 of adenocarcinoma (8.9%), and 117 of mixed or unspecific type (8.9%). The analysis concerns only patients with Kreyberg I or Kreyberg II cancers and the matched controls: There were 1,217 cases and 1,915 controls.

Two controls, selected by searching acceptable records in different units, were matched to each case by sex, age (±5 yr), hospital of admission, and interviewer (*20*). During the last year of the study, cases more than 60 years old, who were widely represented in the sample, were matched to only 1 control (9%). A short lapse time before or after the interview of the case was required. The population of eligible controls consisted of patients hospitalized for non-tobacco-related diseases. This requirement excluded patients with cancers of the respiratory tract, esophagus, liver, pancreas, bladder, and kidneys, and patients with myocardial infarction, other cardiovascular diseases, gastric ulcers, and chronic bronchitis. In addition, patients with alcoholic cirrhosis were excluded. Because of this required condition and of the matching criteria, all eligible controls present in participating units at the time of the interviewer visit were included and the vast majority agreed to participate. Seven percent of the total number of interviewed controls were found unacceptable according to the eligibility criteria. However, 64 controls (3.3%) with tobacco-related disease or liver cirrhosis have been included and were not excluded from the analysis. Among the 1,915 controls, the main diagnostic categories were: trauma (13.8%), osseous diseases (12.9%), viral and other infective diseases (11.1%), benign tumors (10.2%), malignant tumors (8.1%), neurological diseases (7.3%), and digestive diseases (7.1%).

The questionnaire included questions about places of residence since birth (urban or rural), educational level (number of school years since the beginning of education), occupations, smoking, and drinking habits. Risks associated with the various measures of exposure to exclusive cigarette consumption will be detailed. Smokers were defined as people having smoked at least one cigarette per day during at least 1 year.

The following data were collected for each smoker: Age at the first cigarette, depth and frequency of inhalation, the four most recent cigarette brands habitually smoked (which were found to be sufficient to describe the total smoking life of a cigarette smoker), and, for each, the daily consumption and the duration of smoking. Each brand was classified either as light or dark type according to its constituting varieties of tobacco and to the way these tobaccos were cured; these data were provided by the experts of the French tobacco monopoly. Ex-smokers were defined as people who had stopped smoking at least 1 year before the interview. For each ex-smoker, the age of final cessation was noted in addition to the data above. The daily consumption has been calculated by dividing the total life-long number of cigarettes smoked by the overall duration of smoking in days.

Analytical method.—Percentages were compared by the χ^2-test. RR of lung cancer have been estimated with the Mantel-Haenszel method (*21*), and 95% CI with the use of the Cornfield method (*22*). The different parameters characterizing the smoking habits have been analyzed by matched logistic regression (*20*).

RESULTS

Patients with cancer of Kreyberg type I were significantly older ($P<.001$) and had had significantly less education than those with cancer of Kreyberg type II or than the controls (table 1).

The percentage of regular smokers was, of course, significantly greater ($P<.001$) among cases than among controls. Moreover, it was significantly higher ($P<.01$) in Kreyberg I cases (97.8%) than in Kreyberg II cases (92.4%). The RR of smokers relative to nonsmokers in these two types of lung cancer cases were 17.2 ($P<.0001$) and 3.6 ($P<.001$), respectively (table 2). In both types, the risks

TABLE 1.—*Distribution of 1,217 cases and 1,915 controls according to age at diagnosis and educational level*

Variables	Percent of subjects			
	Kreyberg I cell (n = 1,098)	Controls (n = 1,730)	Kreyberg II cell (n = 119)	Controls (n = 185)
Age at diagnosis, yr				
<40	1.8	2.1	4.2	7.0
40-49	15.9	18.3	21.8	22.2
50-59	34.7	37.6	37.8	39.4
60-69	32.2	25.9	30.3	21.1
≥70	15.4	16.1	5.9	10.3
Mean age (±2 SEM)	59.1 (0.6)	58.2 (0.5)	55.8 (1.9)	55.1 (1.6)
Education, yr				
<8	68.0	59.6	62.2	64.3
8-13	25.7	30.0	23.5	25.4
≥14	6.3	10.4	14.3	10.3
Mean yr (±2 SEM)	6.6 (0.3)	7.4 (0.2)	7.7 (0.9)	6.7 (0.8)

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TABLE 2.—*RR of smokers to nonsmokers according to age at diagnosis*[a]

Variables	Kreyberg I lung cancer			Kreyberg II lung cancer		
	No. of cases	No. of controls	RR[b] (95% CI)	No. of cases	No. of controls	RR[b] (95% CI)
Nonsmokers	24	481	1.0	9	42	1.0
Smokers	1,074	1,249	17.2 (11.2–26.3)	110	143	3.6 (1.6–8.3)
Age, yr						
<50	190	264	14.4 (9.0–23.3)	27	40	3.2 (1.2–8.3)
50–59	379	476	16.0 (10.2–25.2)	42	62	3.2 (1.3–7.8)
60–69	341	319	21.4 (13.6–34.1)	36	28	6.0 (2.3–15.9)
≥70	164	190	17.3 (10.6–27.9)	5	13	1.8 (0.4–7.4)

[a] Linear trend tests: $P<.01$ for both Kreyberg categories.
[b] All RR were calculated versus nonsmokers.

increased significantly ($P<.01$; linear trend tests) with the age at diagnosis (table 2).

The separate studies of the different parameters measuring the exposure to cigarettes showed an increased risk of lung cancer in smokers compared to nonsmokers for the following parameters: age at first cigarette, daily consumption, frequency of inhalation, and duration of smoking. Trend tests have appeared to be highly significant for each of these four variables ($P<.0001$) for the Kreyberg I and Kreyberg II type cancers, except for the age at the first cigarette, which is not significantly different in Kreyberg II cases from matched controls. In contrast, a decreased risk was noted among ex-smokers compared to current smokers, which was dependent on the number of years since cessation; the trend test was significant ($P<.0001$) (table 3).

In this study, most smoker cases (90.5%) and controls (85.2%) have smoked dark tobacco exclusively; furthermore, among these smokers, 58% have smoked exclusively the French brand "Gauloise." The percentage of lifelong dark tobacco use among cases (90.3) was higher ($P<.001$) than among the matched controls (84.8); there was no difference between Kreyberg I (90.5) and Kreyberg II (88.2) cases. The RR of Kreyberg I type lung cancer for dark tobacco smokers is 3.7 times higher ($P<.001$) than the risk for exclusive smokers of light tobacco.

The excess of risk for exclusive hand-rolled cigarette smokers versus exclusive manufactured cigarette smokers (RR=1.3) is not significant.

For the study of the role of the filter, exclusive smokers of nonfilter cigarettes have been compared to exclusive smokers of filter cigarettes. Among the Kreyberg I cancer

TABLE 3.—*RR according to characteristic variables of cigarette consumption*

Variables	Kreyberg I lung cancer			Kreyberg II lung cancer		
	No. of cases	No. of controls	RR[a] (95% CI)	No. of cases	No. of controls	RR[a] (95% CI)
Nonsmokers	24	481	1.0	9	42	1.0
No. of cigarettes/day						
1–9	54	182	6.0 (3.5–10.2)	28	45	2.9 (1.1–7.5)
10–14	125	227	11.0 (6.8–18.1)			
15–20	449	512	17.6 (11.3–27.7)	41	65	2.9 (1.2–7.3)
21–39	271	206	26.4 (16.5–42.4)	41	33	5.8 (2.3–15.0)
≥40	175	122	28.8 (15.6–47.4)			
Frequency of inhalation						
None	268	433	12.4 (7.8–19.7)	16	36	2.1[b] (0.8–5.8)
Moderate	97	134	14.5 (8.7–24.3)	94	107	4.1 (1.8–9.6)
Deep	709	682	20.8 (13.4–32.6)			
Duration of smoking, yr						
1–25	90	283	6.4 (3.9–10.5)	55	93	2.8 (1.2–6.6)
26–35	345	396	17.5 (11.1–27.7)			
36–45	365	360	20.3 (12.9–32.2)	55	50	5.1 (2.1–12.7)
>45	274	210	26.2 (16.4–42.0)			
Age at first cigarette, yr						
≤16	342	341	20.1 (12.8–31.9)	69	79	4.1 (1.8–9.7)
17–19	311	373	16.7 (10.6–26.5)			
20–24	323	398	16.3 (10.3–25.8)	41	64	3.0 (1.2–7.4)
≥25	98	137	14.3 (8.6–24.0)			
Time since cessation, yr						
1–3	132	77	34.6 (20.4–58.4)	13	9	6.7 (2.0–24.2)
4–6	56	92	12.2 (7.0–21.4)	8	18	2.1[b] (0.6–7.2)
7–10	41	75	10.9 (6.1–19.9)			
11–19	39	125	6.3 (3.5–11.2)	4	21	1.0[b] (0.2–3.7)
≥20	17	82	4.2 (2.0–8.5)			

[a] All RR were calculated versus nonsmokers.
[b] Not significant.

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TABLE 4.—*RR according to type of tobacco and to use of hand-rolled and filter cigarettes in Kreyberg I cell lung cancer*

Variables	No. of cases	No. of controls	RR[a] (95% CI)
Nonsmokers	24	481	1.0
Type of tobacco			
Light	15	61	4.9 (2.3–10.4)
Mixed	83	110	15.1 (8.9–25.7)
Dark	976	1,078	18.1 (11.7–28.3)
Use of hand-rolled cigarettes			
Never	830	1,040	16.0 (10.3–24.9)
Mixed	154	118	26.2 (15.9–43.3)
Yes	90	91	19.8 (11.7–33.9)
Use of filter cigarettes			
Yes	90	166	10.9 (6.5–18.2)
Mixed	288	312	18.5 (11.7–29.5)
Never	696	771	18.1 (11.7–28.3)

[a] RR were calculated versus nonsmokers.

cases, the RR for lifetime nonfilter cigarette users was 1.7 times greater ($P<.001$) than the risk for lifetime filter cigarette users (table 4). Long-term smokers and long-term quitters are more often lifelong nonfilter cigarette smokers. The excess of risk for nonfilter compared to filter cigarette smokers was not significantly increased (RR = 1.28) when duration of smoking and years since cessation were taken into account; risk associated with use of filter cigarettes is confounded by these two variables.

All these risks could not be estimated among Kreyberg II cases because of the small size of the sample.

The evolution of RR of lung cancer with duration of smoking and daily consumption has been estimated among lifelong light and dark cigarette smokers separately (excluding ex-smokers). Table 5 shows the evolution in light and dark tobacco smokers: In dark tobacco smokers, risks are increased both with duration of smoking and with daily consumption. Moreover, when the risks could be estimated among light cigarette smokers, those observed among dark compared to light are increasingly greater in each class of duration and daily consumption. A similar analysis was performed among lifelong filter and nonfilter cigarette smokers; as seen in table 6, in each of these two categories of smokers, RR increase with duration of smoking and daily consumption. In each daily consumption and duration of smoking category, the risk for nonfilter cigarette smokers is greater than that for filter cigarette smokers. Similar results were found when the categories of exclusive hand-rolled and exclusive manufactured cigarette smokers were compared. Risks were higher for hand-rolled cigarette smokers than for manufactured cigarette smokers (table 7).

The main purpose of this paper was to study the effect of filter use and type of tobacco on lung cancer. All the parameters described above were studied together in a matched logistic model that took into account all the variables for the Kreyberg I category. This method allowed the estimation of RR for each variable when adjusting for the others. For all these covariates, the risks have been verified to be multiplicative. Social class was also introduced in the logistic model by the creation of 3 categories on the basis of the patients' occupations reflecting their educational level: low (unskilled manual), medium (unskilled nonmanual), and high (skilled). The analysis performed among both smokers and nonsmokers (1,047 cases and 1,730 matched controls) allowed us to determine the characteristics of the less exposed category of smokers, i.e.: 1–9 cigarettes per day, 1–25 years of smoking, no inhalation, light, filter and manufactured cigarette smokers, ex-smokers, and high social class. The excess risk associated with age at first cigarette was not significant when duration of smoking was introduced in the model. These two variables being strongly correlated, only duration of smoking was considered in the model. The excess risk for this less exposed category versus nonsmokers was 1.41 ($P<.0001$).

The second analysis consisted of the study of the parameters among smokers. Table 8 shows the contribution of each covariate introduced in this model. All the adjusted RR have been estimated versus the less exposed category of smokers defined above. A total of 868 strata composed of 868 Kreyberg I cases and 1,473 matched controls has been considered. The 206 cases who had to be excluded because their matched controls did not satisfy the required criteria (exclusive cigarette smokers) were verified to have had the same characteristics and smoking behavior as those who remained in the analysis.

It appears that the following covariates are significantly associated with lung cancer: daily consumption ($P<.0001$), duration of smoking habit ($P<.0001$), frequency of inhalation ($P<.0001$), social class ($P<.0001$), and type of tobacco ($P<.02$). An excess of risk, although not statistically significant, was associated with nonfilter use (RR = 1.23; $P<.11$), use of hand-rolled cigarettes

TABLE 5.—*RR[a] of lung cancer according to type of tobacco by duration of smoking and daily consumption among current smokers in Kreyberg I cell lung cancer*

Daily consumption, No. of cigarettes	Duration of cigarette smoking, yr											
	Light				Mixed				Dark			
	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45
1–14	—	8.0	—	—	10.0	5.0	2.5	4.0	3.2	9.4	11.6	14.9
15–20	—	20.0	—	—	15.1	10.6	16.0	10.0	7.5	21.5	17.9	28.9
≥21	10.0	20.0	—	—	60.1	21.9	36.1	15.0	23.5	27.1	57.3	48.1

[a] RR were calculated versus nonsmokers.

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TABLE 6.—*RR*[a] *of lung cancer according to use of filter by duration of smoking and daily consumption among current smokers in Kreyberg I cell lung cancer*

Daily consumption, No. of cigarettes	Duration of cigarette smoking, yr											
	Filter				Mixed				Nonfilter			
	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45
1–14	4.0	5.3	6.2	—	—	6.7	11.8	9.5	4.5	12.0	10.7	14.8
15–20	5.0	11.5	15.4	25.1	10.5	17.1	14.5	20.0	8.4	24.5	20.4	32.8
≥21	17.5	11.5	25.1	50.1	23.1	27.0	66.4	31.2	20.0	30.8	47.0	49.0

[a] RR were calculated versus nonsmokers.

(RR = 1.22; $P < .07$), and current use (RR = 1.20; $P < .06$). The results were similar when ex-smokers were excluded of the model; moreover, the excess risk associated with nonfilter use was significant (RR = 1.24; $P < .02$).

DISCUSSION

The results of a French study which is part of a large international case-control study on lung cancer are described. General critical comments of the protocol have been presented in a recent paper on the complete set of international data (*16*); however, the lack of a histologic concordance study among French hospitals must be noted.

A large number of epidemiologic studies (*23–25*) have shown a strong association between cigarette consumption and Kreyberg I lung cancer among males. For adenocarcinoma (Kreyberg II cases), the risk was found to be increased by some authors (*23–25*), and unchanged by others (*26, 27*). In our study, the risk of lung cancer associated with cigarette consumption was increased not only for Kreyberg I category (RR = 17.2) but also, less strongly, for adenocarcinoma (RR = 3.6).

In this study, although the regression results must be interpreted cautiously because of the correlations among many of the smoking-related variables (*28*), all the usual covariates measuring cigarette exposure have been found to be significantly associated with Kreyberg I lung cancer. The lack of significance for nonfilter versus filter cigarette smokers (RR = 1.23) when smokers and ex-smokers are included in the model may be explained by the fact that long-term quitters are more often lifelong nonfilter cigarette smokers; as seen above.

We found a higher risk for dark versus light cigarette smokers among Kreyberg I cases; although the proportion of light cigarette smokers was not too high (3.4%), this excess risk (RR = 1.94) persisted after accounting for the other covariates that measure the cigarette exposure in a logistic model. These results fit the hypothesis of a more harmful effect of dark tobacco compared to light tobacco (*29*) recently supported by an epidemiologic study conducted in Cuba (*15*).

The increased risk of lung cancer associated with dark tobacco can be contrasted to the low rate of death by lung cancer seen in France—where most cigarette smokers use dark tobacco—as opposed to other European countries and the United States, where light tobacco is smoked usually. For example, in 1976 the death rates observed among males in France and in England were around 40 and 75 per 100,000, respectively (world population-standardized mortality rates) (*1*). These statistics can be explained by the study of the mean cigarette sales per adult (i.e., 15 yr old and over), in these countries (*30*): Between 1932 and 1973, the average French sales per adult were about half of that in the United Kingdom and the United States; in 1957, for instance, the sales in France and in England were 1,290 and 2,590 cigarettes per adult, respectively. Moreover, in Italy, where lung cancer mortality is close to that in France, the situation concerning cigarette sales is similar: Most smokers are dark tobacco users and the evolution of the average sales of cigarettes per adult between 1932 and 1973 was almost the same as in France, about 1,000 cigarettes per adult in 1957.

If our results are supported by other epidemiologic studies, an important evolution in the French situation could be expected, since in our country the total sales of light tobaccos increased from 18% in 1976 to about 43% in 1983 (*19*). However, our results need the support of several other studies before we can establish our hypothesis. We

TABLE 7.—*RR*[a] *of lung cancer according to use of hand-rolled cigarettes by duration of smoking and daily consumption among current smokers in Kreyberg I cell lung cancer*

Daily consumption, No. of cigarettes	Duration of cigarette smoking, yr											
	Manufactured				Mixed				Hand-rolled			
	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45	1–25	26–35	36–45	>45
1–14	3.8	7.7	7.3	9.4	—	28.1	27.6	20.0	—	5.0	13.4	16.7
15–20	7.5	19.3	17.3	25.3	10.0	22.6	22.4	24.5	—	33.4	16.0	80.2
≥21	23.3	25.0	53.1	44.6	40.1	60.1	37.9	36.1	—	40.0	35.1	50.1

[a] RR were calculated versus nonsmokers.

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TABLE 8.—*Results of the multivariate analysis of characteristic parameters of smoking habits among smokers in Kreyberg I cell lung cancer*

Variables	Log likelihood	RR (95% CI)	*P*-value for trend test
No variable	−745.2		
All variables	−640.8		
No. of cigarettes smoked/day	−684.8[a]		<.0001
1–9		1.00	
10–14		2.10 (1.31–3.36)	
15–20		3.22 (2.10–4.93)	
21–39		5.24 (3.31–8.28)	
≥40		6.08 (3.71–9.97)	
Duration of smoking, yr	−652.8[a]		<.0001
1–25		1.00	
26–35		2.60 (1.78–3.81)	
36–45		3.21 (2.09–4.92)	
≥46		3.52 (2.09–5.92)	
Inhalation	−647.1[a]		<.0001
Never		1.00	
Mostly		1.08 (0.74–1.58)	
Always		1.44 (1.14–1.82)	
Social class	−646.6[a]		<.0001
High		1.00	
Medium		1.15 (0.86–1.54)	
Low		1.59 (1.17–2.15)	
Type of tobacco	−643.1[a]		<.02
Light		1.00	
Mixed		1.55 (0.71–3.42)	
Dark		1.94 (0.95–3.96)	
Current use	−642.0[a]		<.06
No		1.00	
Yes		1.20 (0.93–1.54)	
Use of hand-rolled	−642.0[a]		<.07
Never		1.00	
Mixed		1.32 (0.95–1.81)	
Always		1.22 (0.83–1.79)	
Use of filter	−642.0[a]		<.11
Always		1.00	
Mixed		1.09 (0.74–1.58)	
Never		1.23 (0.87–1.73)	

[a] Value represents the log likelihood function when the corresponding covariate is removed from the "all variables" model.

expect the most relevant support to come from the results obtained in the other countries participating in this study, especially from Italy.

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CARDIOVASCULAR AND OTHER DISEASES IN SMOKERS OF LOW YIELD CIGARETTES

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Abstract—The association of smoking low yield cigarettes with the risk of cancer, cardiovascular disease, and other disease associated previously with smoking is controversial. In 1979 we began a prospective epidemiologic study of this subject. We here report on the first 4 years of follow-up in the 16,270 current, regular cigarette smokers and the 42,113 subjects who never used any form of tobacco enrolled in the study. In multivariate analyses that included age, sex, race, number of cigarettes smoked per day and other factors related to cardiovascular disease, the risk of cardiovascular diseases was consistently higher in smokers of higher than in smokers of lower yield cigarettes, although the magnitude of the difference in risk was very small. The risks of cancer of the trachea, bronchus and lung, of all smoking-related cancers as a group, of diseases of the respiratory system, and of peptic ulcer diseases were not significantly associated with yield in smokers. The incidence rates of cardiovascular diseases considered as a group, cancer of the trachea, bronchus, and lung and all smoking-related cancers were higher in smokers of low yield cigarettes than in never users of any form of tobacco. We conclude that the smoking of low yield cigarettes is not without associated hazard. On the other hand, the results suggest that smokers who cannot quit might best use the least number of the lowest yield cigarette.

INTRODUCTION

MOST epidemiologic studies of the subject have shown that smokers of cigarettes with low yields of tar and nicotine have a lower risk of cancers of the trachea, bronchus and lung [1–5] compared with smokers of high yield cigarettes. The results of studies of the association of smoking cigarettes having a low yield of tar and nicotine with cardiovascular disease have been inconsistent [1–3, 6–8], whereas diseases other than cancer and cardiovascular disease are largely unstudied [9]. In 1979, we began a prospective epidemiologic study of the health risks associated with smoking low yield cigarettes. We here report the results of an analysis of the incidence of hospitalization for cardiovascular and other diseases after 4 years of follow-up in the 16,270 current, regular cigarette smokers and 42,113 never users of any form of tobacco who were enrolled in this study.

MATERIALS AND METHODS

Study subjects were members of the Kaiser-Permanente Medical Care Program who had multiphasic health checkups in either the Oakland or San Francisco facilities between July 1979 and 31 December 1982 and completed research questionnaires on past and current tobacco use. Any member of the Health Plan may have a health check-up, but only a small percentage take advantage of this opportunity. Other studies have shown that persons

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taking check-ups are generally representative of all adult Health Plan members. This analysis is based on the 42,113 never users of any form of tobacco and the 16,270 current, regular cigarette smokers who used no other form of tobacco; smoked a single brand of cigarette at the time of their interview for the study; provided sufficient information so that the tar and nicotine yield of their cigarette could be determined; and gave the number of cigarettes they smoked. A total of 2524, current regular smokers were excluded by the above criteria. Eight hundred and ninety three were excluded because they smoked more than one brand of cigarettes, 179 because the number of cigarettes per day was unknown, 715 because information on tar and nicotine for the brand they smoked was not measured by the Federal Trade Commission (mostly foreign cigarettes), and 737 because the brand information supplied was incomplete.

The tar and nicotine yield of the subjects' currently smoked cigarette was determined using the 1979 Federal Trade Commission Report [10], or, for cigarette brands and types first marketed after 1979, the most recent Federal Trade Commission report. For some analyses, cigarette yield was dichotomized into a high and low group. Low yield cigarettes were defined as those with less than 15.0 mg of tar and less than 1.0 mg of nicotine. All other cigarettes were considered high yield.

Information on a history of heart disease, stroke, diabetes and treated hypertension and on use of alcohol was gotten from other questionnaires completed by study subjects the day of their checkup. Quetelet's body mass index was calculated from measured height and weight according to the formula—Quetelet's body mass index equals $(100 \times \text{weight})/(\text{height}^2)$. Serum cholesterol was determined from a blood specimen drawn the day of the checkup. Blood pressure was measured by an automatic sphygomanometer.

Hospitalizations in Northern California Kaiser-Permanente facilities after entry to the study and through 31 December 1982 were ascertained using computer-stored hospital discharge records. Only the principal discharge diagnosis was used in the analysis. When a subject was hospitalized more than once for a given diagnosis, we considered only the first admission for that diagnosis. When a subject was hospitalized with more than one specific cardiovascular diagnosis, the subject's hospitalizations were counted in the analysis of each of the separate diagnostic categories, but only once for categories based on several cardiovascular diagnoses. For this reason, the total number of events for categories based on several cardiovascular diagnoses may be less than the sum of the number of events for the individual diagnoses.

The denominators for the calculation of the incidence rates were obtained using computer-stored membership records to determine in every month after entry whether the subject was a member of the medical care program. We then cumulated the number of person-months of membership and divided by 12 to obtain person-years. We used the direct method to adjust for age. The entire population of current smokers and never tobacco users was used as the standard for the age adjustment.

We used the Cox proportional hazards model [11] as implemented on the Statistical Analysis System [12] in the multivariate analyses. Observation was censored when subjects left the Health Plan or on 31 December 1982 if they had not been hospitalized for the disease under consideration by that date. Relative risks were estimated from the results of this model and approximate 95% confidence limits were calculated. When these confidence limits exclude 1.00, the estimated relative risk is significantly ($p < 0.05$) associated with the examined factor.

RESULTS

Fifty-six percent of subjects in the study were female and 44% male. Among current smokers, 69% smoked high yield cigarettes and 31% low yield. Table 1 shows selected characteristics of smokers of high compared with low yield cigarettes.

Table 2 shows the age-adjusted rates of several cardiovascular disease categories in smokers of high and low yield cigarettes separately by sex and the number of cigarettes smoked per day. The relative risks of the diseases in smokers of high compared with low

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TABLE 1. SELECTED CHARACTERISTICS OF SMOKERS OF HIGH AND LOW YIELD CIGARETTES

	High yield	Low yield
Sex—N (%)		
Male	1894 (38.6)	5332 (46.9)
Female	3018 (61.4)	6026 (53.1)
Age—N (%)		
< 30	1181 (24.0)	2814 (24.8)
30–39	1457 (29.7)	3211 (28.3)
40–49	827 (16.8)	2230 (19.6)
50–59	817 (16.6)	1900 (16.7)
60+	630 (12.8)	1203 (10.6)
Cigarettes per day ~ N (%)		
< 10	657 (13.4)	1747 (15.4)
10–24	2647 (53.9)	6735 (59.3)
25+	1608 (32.7)	2876 (25.3)
Race—N (%)		
Not black	3786 (77.1)	6703 (59.0)
Black	1126 (22.9)	4655 (41.0)
Age at which smoking started —mean (SD)	19.3 (5.3)	18.8 (5.4)
Mean number of years smoked —mean (SD)	20.6 (12.9)	20.3 (12.6)

Percentages may not add to 100.0 because of rounding.

yield cigarettes are also shown. The table includes all of the cardiovascular disease categories in which more than 10 smokers were hospitalized after entry. Although the number of events is small in some groups and the rates therefore somewhat unstable, a pattern of higher risk of cardiovascular disease in smokers of high yield cigarettes is evident, particularly in men who smoked at least 10 cigarettes per day.

Table 3 shows the results of successive multivariate analyses of the five cardiovascular disease categories among the current, regular cigarette smokers. To take advantage of the greater statistical power of using yield as a continuous variable, this variable, as well as age and number of cigarettes smoked per day, were included as continuous variables in these and subsequent multivariate analyses. The other variables included in the models were sex, race (black or other) and number of cigarettes smoked per day.

In the first column of the table, all the current, regular smokers were included in the analyses. We show the estimated increase in the relative risk of each of the disease categories per 5.0 mg increase in tar yield. Tar and nicotine are highly correlated ($r = 0.93$) and other analyses in which we included nicotine instead of tar yield in the regression model gave virtually identical results. The table shows that the relative risk of cardiovascular disease is significantly ($p < 0.05$) higher in smokers of higher tar cigarettes in each of the five categories except other ischemic heart disease.

To rule out the possibility that a tendency of people with a history of cardiovascular disease to switch to higher yield cigarettes might account for these findings, we did multivariate analyses in which subjects with a history of heart disease or stroke at entry to the study were excluded. Age, sex, race, number of cigarettes per day and tar were included as covariates as before. The second column of the table shows that the relative risk of cardiovascular disease remains significantly ($p < 0.05$) higher in smokers of higher tar cigarettes in each category except other ischemic heart disease even after excluding subjects with a prior history of heart disease or stroke. In fact, the relative risk estimates for tar are slightly higher after excluding these subjects, implying that there is a tendency of people with such histories to smoke cigarettes with lower tar yields.

To rule out the possibility that differences in other known cardiovascular risk factors between smokers of higher and lower yield cigarettes might explain our results, we did analyses in which subjects with a past history of heart disease or stroke were excluded, and Quetelet index, serum cholesterol, a history of treated hypertension, diabetes and use of alcohol were used as covariates along with age, sex race, number of cigarettes smoked

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TABLE 2. AGE-ADJUSTED RATES[1] AND RELATIVE RISKS OF SEVERAL CARDIOVASCULAR DISEASE CATEGORIES IN SMOKERS OF HIGH AND LOW YIELD CIGARETTES BY SEX AND NUMBER OF CIGARETTES SMOKED PER DAY (NUMBER OF PEOPLE WITH EVENTS IN PARENTHESES)

	Cigarettes per day					
	< 10		10–24		25 +	
Category	High yield	Low yield	High yield	Low yield	High yield	Low yield
			Men			
All diseases of the cardiovascular system[3]	5.5 (5)	5.3 (1)	11.3 (60)	9.2 (17)	16.1 (154)	10.0 (16)
Relative risk[2]	1.0		1.2		1.6	
Any atherosclerotic disease[4]	4.4 (4)	5.3 (1)	6.8 (36)	3.6 (6)	9.7 (34)	4.3 (7)
Relative risk[2]	0.8		1.9		2.2	
Acute myocardial infarction[5]	1.1 (1)	0.0 (0)	3.6 (19)	0.9 (2)	5.5 (19)	1.8 (3)
Relative risk[2]	—		3.9		3.0	
Other ischemic heart disease[6]	4.4 (4)	5.3 (1)	4.1 (22)	3.1 (5)	4.5 (16)	1.9 (3)
Relative risk[2]	0.8		1.3		2.4	
Thromboembolic stroke and TIA[7]	1.1 (1)	0.0 (0)	1.7 (9)	0.9 (2)	1.2 (4)	0.6 (1)
Relative risk[2]			1.8		1.9	
			Women			
All diseases of the cardiovascular system[3]	7.9 (13)	2.7 (2)	8.4 (54)	6.0 (20)	9.8 (21)	8.0 (14)
Relative risk[2]	2.9		1.4		1.2	
Any atherosclerotic disease[4]	2.6 (4)	0.0 (0)	3.4 (22)	1.7 (6)	3.6 (8)	5.1 (9)
Relative risk[2]	—		2.0		0.7	
Acute myocardial infarction[5]	0.7 (1)	0.0 (0)	1.6 (10)	0.9 (3)	0.6 (1)	2.6 (4)
Relative risk[2]	—		1.8		0.2	
Other ischemic heart disease[6]	1.9 (3)	0.0 (0)	1.6 (10)	0.9 (3)	2.7 (6)	2.6 (5)
Relative risk[2]	—		1.8		1.0	
Thromboembolic stroke and TIA[7]	0.0 (0)	0.0 (0)	0.6 (4)	0.9 (3)	1.0 (2)	0.0 (0)
Relative risk[2]	—		0.7		—	

[1]Per 1000 person-years.
[2]In smokers of high yield compared with low yield cigarettes.
[3]ICDA-8 Codes 390–458.
[4]Includes acute myocardial infarction, other ischemic heart disease, hemorrhagic stroke, thromboembolic stroke and TIA, non-syphilitic aortic aneurysm, peripheral vascular disease.
[5]ICDA-8 Code 410.
[6]ICDA-8 Codes 411–414.
[7]ICDA-8 Codes 432–435.

TABLE 3. ESTIMATED RELATIVE RISK OF CARDIOVASCULAR DISEASE PER 5.0 mg INCREASE IN TAR AMONG CURRENT, REGULAR CIGARETTE SMOKERS

	Model		
Disease category	All[1] (95% confidence limits)	Prior HD removed[2] (95% confidence limits)	Prior HD removed;[3] all available risk factors (95% confidence limits)
All diseases of the cardiovascular system	1.15 (1.05, 1.27)	1.18 (1.06, 1.32)	1.15 (1.03, 1.29)
Any atherosclerotic disease	1.19 (1.04, 1.36)	1.23 (1.05, 1.43)	1.19 (1.01, 1.40)
Acute myocardial infarction	1.22 (1.00, 1.50)	1.29 (1.03, 1.61)	1.25 (0.99, 1.58)
Other ischemic heart disease	1.17 (0.97, 1.40)	1.21 (0.98, 1.50)	1.18 (0.94, 1.48)
Thromboembolic stroke and TIA	1.41 (1.02, 1.94)	1.62 (1.07, 2.47)	1.74 (1.12, 2.69)

[1]Age, sex, race and number of cigarettes per day included as covariates.
[2]Subjects with prior history of heart attack or stroke excluded; age, sex, race and number of cigarettes per day included as covariates.
[3]Subjects with prior history of heart attack or stroke excluded; age, sex, race, number of cigarettes per day, Quetelet index, serum cholesterol, history of hypertension and alcohol consumption included as covariates.

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TABLE 4. ESTIMATED RELATIVE RISK OF OTHER SMOKING RELATED DISEASES PER 5.0 mg INCREASES IN TAR AMONG CURRENT, REGULAR CIGARETTE SMOKERS

Category	N of cases	Estimated relative risk[1] (95% confidence limits)
Cancer of the trachea, bronchus and lung	35	0.87 (0.68, 1.11)
All smoking related cancers[2]	61	0.91 (0.76, 1.10)
All diseases of the respiratory system	110	0.97 (0.84, 1.13)
Peptic ulcer disease	21	0.85 (0.61, 1.17)

[1]Per 5.0 mg increase in tar controlling by the Cox regression technique for age, sex, race, and number of cigarettes smoked per day.
[2]Trachea, bronchus, lung, larynx, pharynx, esophagus, pancreas, kidney, bladder, cervix.

per day and tar. The third column of the table shows that, after controlling by the Cox regression technique for differences in these known cardiovascular risk factors for which we have information, the relative risk remains significantly ($p < 0.05$) higher in smokers of higher tar cigarettes for all cardiovascular disease as a group, for any atherosclerotic disease and for thromboembolic stroke and transient ischemic attacks. The probability value approaches significance for acute myocardial infarction ($p = 0.06$) but is not significant for other ischemic heart disease ($p = 0.16$).

We also did multivariate analyses of these diseases including the measured diastolic blood pressure rather than a history of treated hypertension as a covariate along with the other known cardiovascular risk factors. The results of these analyses were virtually identical to the ones we present in column 3 of Table 2.

Table 4 shows the results of multivariate analysis of cancer of the trachea, bronchus and lung; all smoking related cancers; diseases of the respiratory system; and peptic ulcer disease in current regular cigarette smokers. There is no statistically significant association of yield with any of these disease categories after controlling by this multivariate technique for age, race, sex and number of cigarettes smoked per day.

Table 5 shows the age-adjusted rates of cardiovascular disease, cancer of the trachea, bronchus and lung, all smoking related cancers and diseases of the respiratory system in smokers of low yield cigarettes compared with subjects who never used any form of tobacco separately in men and women. The relative risks of the diseases in smokers of low yield cigarettes compared with never users of any form of tobacco are also shown. Both the rates and the relative risks are generally higher in smokers of low yield cigarettes than in never users of tobacco.

DISCUSSION

In this study, smokers of higher yield cigarettes had a significantly higher risk of all cardiovascular disease considered as a group, whereas yield was not significantly associated with the risk of several other diseases related to cigarette smoking in previous studies. The relative risks do not show a completely consistent pattern, especially in women (Table 1) and where increased, they are so small in magnitude as to leave open the possibility that unaccounted for bias may explain them.

The small number of hospitalizations for cancer of the trachea, bronchus and lung and for peptic ulcer disease may account for the absence of a relation of yield to these conditions in our population. More important, the results must be interpreted recognizing the limitations imposed by using in the analysis yield at the time the study questionnaires were completed rather than a life-time estimate of total exposure to tar, nicotine, or another component of cigarette smoke. This feature of the study design means the data we present on the association of smoking low yield cigarettes with diseases such as lung cancer, in which risk in smokers is probably a function of exposure in the distant past,

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TABLE 5. AGE-ADJUSTED RATES AND RELATIVE RISKS OF SEVERAL DISEASES IN SMOKERS OF LOW YIELD CIGARETTES COMPARED WITH NEVER USERS OF ANY FORM OF TOBACCO BY SEX (NUMBER OF EVENTS IN PARENTHESES)

	Men		Women	
Category	Low yield	Never tobacco	Low yield	Never tobacco
All disease of the cardiovascular system	11.8 (34)	9.6 (237)	7.8 (36)	5.8 (316)
Relative risk[1]	1.2		1.3	
Any atherosclerotic disease	4.8 (14)	4.8 (118)	3.5 (15)	2.2 (123)
Relative risk[1]	1.0		1.5	
Acute myocardial infarction	1.9 (5)	2.4 (59)	1.4 (7)	0.8 (44)
Relative risk[1]	0.8		1.8	
Other ischemic heart disease	3.1 (9)	2.9 (72)	1.9 (8)	1.7 (93)
Relative risk[1]	1.0		1.1	
Thromboembolic stroke and TIA	1.2 (3)	0.7 (17)	0.7 (3)	0.5 (27)
Relative risk[1]	1.7		1.4	
Lung cancer	1.5 (4)	0.2 (4)	2.0 (10)	0.1 (5)
Relative risk[1]	9.0		21.7	
All smoking related cancer[2]	3.0 (8)	0.6 (15)	2.9 (14)	0.2 (12)
Relative risk[1]	4.8		13.1	
All diseases of the respiratory system	5.0 (15)	2.6 (70)	4.3 (22)	1.8 (91)
Relative risk[1]	1.9		2.5	

[1]In smokers of low yield cigarettes (< 15.0 mg of tar and < 1.0 mg of nicotine) compared with never users of any form of tobacco.
[2]Cancers of the trachea, bronchus, lung, larynx, pharynx, esophagus, pancreas, kidney, bladder and cervix.

should be viewed with particular caution. It is possible, for example, that smokers of lower yield cigarettes in 1980 were smokers of very high yield cigarettes earlier in life and switched because of symptoms that were indications of damage to the lungs that presaged cancer. The risk of cardiovascular disease in smokers, if causal, is most likely a function of recent levels of exposure to the component of cigarette smoke that affects disease. Thus, the study's results for cardiovascular disease are not subject to limitation in interpretation for this reason. It is of note that smoking more cigarettes per day was associated with significantly higher risk of all of the disease categories shown in Table 3 (data available from the authors upon request).

Previous studies [1–3, 6–8] have examined the relation of the smoking of lower yield cigarettes to the risk of cardiovascular disease. Hammond *et al.* [1], Dean *et al.* [2] and Higgenbottom *et al.* [3] found a significant association of cardiovascular disease risk in smokers with yield. In contrast, Castelli *et al.* [6]. Kaufman *et al.* [7] and Hawthorne and Frye [8] found no significant association of yield with the risk of coronary heart disease. We do not have an explanation for the discrepancies in the results of these studies. However, it should be noted that the studies differed in their definitions of high and low yield; in the diseases studied, in the time periods covered, and in the manner and extent to which possible differences in other cardiovascular risk factors between smokers of low and high yield cigarettes were accounted for in the analysis. Also, to determine the tar and nicotine yield of cigarettes smoked by subjects in our study, we considered not only the brand of the cigarette and whether or not it was filtered but also its size and whether or not it was mentholated. Within a single brand of filtered cigarettes, the tar ratings can vary by as much as 3.5 mg per cigarette depending on the size of the cigarette and whether or not it is mentholated. If tar and nicotine are determined solely using information on brand name and whether or not the cigarette is filtered, as may have been done in some of the other studies, there will be some misclassification of tar and nicotine yield for smokers, and this misclassification would tend to obscure associations with disease. On the other

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hand, it is possible that in our population some other factor related to risk of cardiovascular disease such as exercise or diet differs systematically between smokers of higher and lower yield cigarettes and thus accounts for our results.

In our analyses, we present the association of risk with tar yield rather than the yields of nicotine or carbon monoxide even though nicotine and carbon monoxide but not tar have been postulated to be the mediators of the increased risk of cardiovascular diseases in cigarettes smokers [13, 14]. We did this because the high correlations of tar, nicotine and carbon monoxide make it impossible to determine the association of risk to one measure of yield independent of the other in this population.

Yield was derived from information provided on self-administered questionnaires. We validated this information and showed that the questionnaires are an accurate source of information on smoking vs non-smoking [15]. They probably are not perfectly accurate with respect to yield. In addition, yields assigned from questionnaires do not necessarily reflect the actual levels of toxic substances in smokers, who are known to compensate for smoking lower yield cigarettes in several ways [16–19]. In addition, some smokers may have switched to higher or lower yield cigarettes in the follow-up period. We estimate from a survey at 1-year of a random sample of subjects in the first year that 78% of smokers do not change the cigarette they smoke at all and that over 90% smoke cigarettes that are within 4 mg of yield of those they smoked at baseline. Most important, all three of these deficiencies of the study would tend to obscure an association of yield with risk. Thus, these facts do not account for our finding of a positive association of yield to the risk of cardiovascular disease but might explain the absence of an association with cancer of the trachea, bronchus, and lung, all smoking related cancers, respiratory disease and peptic ulcer disease.

The outcomes we studied were based on computer-stored discharge records and were limited to hospitalized illness. It is possible that there was some miscoding of the records. Miscoding would also tend to obscure an association of yield with risk. To estimate the extent to which this might be a problem in our study, we determined the validity of the diagnoses of a 20% random sample of cases of cardiovascular disease and all of the cases of cancer of the trachea, bronchus, or lung by record review. Sixty-five of 66 of the reviewed cases of cardiovascular disease and 30 of 31 of the reviewed cases of cancer of the trachea, bronchus, or lung were found to be accurate based on the computer-stored record. Diagnosis considered accurate reflected biopsy proven cases of cancer or cardiovascular disease confirmed by autopsy, angiography, venography, or other objective tests. We conclude that inaccuracy of diagnoses on the computer-stored records do not explain our findings. Because it is unlikely that smokers of low or high yield cigarettes are selectively hospitalized, our exclusive reliance on hospitalizations as outcome measures also is unlikely to result in material bias.

The risks of cardiovascular disease, of cancer of the trachea, bronchus and lung, and of all smoking-related cancers were higher in smokers of low yield cigarettes than in never users of any form of tobacco. The smoking of lower yield cigarettes is not, therefore, without associated hazard. On the other hand, because high yield cigarettes are not associated with less risk of any of these diseases, the results suggest that smokers who cannot quit might best smoke the least number of the lowest yield cigarette.

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Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked

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SUMMARY In a case control study of over 12 000 inpatients aged 35–74, risk of lung cancer, chronic bronchitis, and, particularly in those aged 35–54, ischaemic heart disease was positively associated with the number of manufactured cigarettes smoked daily and was negatively associated with long term giving up. Risk of stroke was not clearly related to smoking. Among manufactured cigarette smokers, lung cancer risk tended to be lowest in those who had always smoked filter cigarettes. This pattern was, however, evident only in men who additionally smoked pipes, cigars or handrolled cigarettes and in women, not being seen in men who smoked only manufactured cigarettes. Risk of lung cancer was not clearly related to time of switch to filter cigarettes. A markedly lower risk of chronic bronchitis was seen in men, but not women, who smoked filter rather than plain cigarettes. Heart disease risk did not vary by type of cigarette smoked 10 years before admission, but, compared with those who had never smoked filter cigarettes, those who had ever smoked filter cigarettes had a higher risk in men and a lower risk in younger women. Compared with the general population, markedly more controls were ex-smokers, suggesting incipient disease, whether or not smoking related, may alter smoking habits, thus affecting the interpretability of the findings. Control smokers were also relatively much more likely to report smoking plain cigarettes than expected. This comparison, not made in other studies relating risk to type of cigarette smoked, indicates that great care must be taken in verifying validity of reported smoking habits. While our findings are compatible with other evidence that risk of lung cancer and chronic bronchitis is probably reduced by switching from plain to filter cigarettes, they underline the difficulties in obtaining valid evidence from epidemiological studies.

In 1950 nearly all British smokers consumed untipped plain cigarettes with mean tar yields of over 30 mg. In 1976, when this study was planned, 88% of cigarettes smoked had filters, and mean tar yields had fallen to around 18 mg; these trends have continued subsequently. By 1976, only four studies[1–4] had compared risks of smoking associated diseases in smokers of high tar plain cigarettes and lower tar filter cigarettes. Only one study, by Dean *et al*,[2] was carried out in the United Kingdom and it used a technique (comparison of smoking habits of decedents obtained second-hand from relatives with those of the living population obtained directly) which is open to criticism. The main aim of the present study was to relate type of cigarette smoked to prevalence of the same four index diagnoses—lung cancer (ICD 162), chronic bronchitis (ICD 491, 492, 496), ischaemic heart disease (ICD 410–414), and 'stroke' (ICD 431–438, excluding subarachnoid haemorrhage)—that Dean had studied. This paper reports the results found and compares them with those from both the earlier studies[1–4] and seven more recent ones.[5–11] A more extensive report is available on request from PNL.

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Methods and response

The overall design was a case control study of hospital inpatients. For each index diagnosis, the intention was to interview 200 cases and 200 matched controls in each of the eight sex/age cells (ie, male or female, and aged 35–44, 45–54, 55–64 or 65–74). This gave a target of 12 800 patients, though

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for some categories (eg, young female chronic bronchitics) this would be unattainable. Patients were selected from medical (including chest medicine), thoracic surgery, and radiotherapy wards in hospitals with a large flow of such patients in major centres in 10 areas of the country. Interviewers visited the wards at regular intervals and selected cases based on provisional diagnosis. Controls were patients without one of the four index diseases, individually matched to cases on sex, age, hospital region, and, when possible, hospital ward and time of interview. The provisional diagnosis of the controls was not recorded; nor, at this stage, were controls with smoking associated diseases other than the four index diseases excluded.

Altogether 12 693 interviews were achieved. The respondent was asked detailed questions on smoking, including brand smoked at admission and 1, 3, 5, and 10 years before admission, and number of cigarettes smoked at these times, at ages 16, 20, 25, and at the age when cigarette smoking was heaviest. Smoking habits at time of disease onset were not directly recorded as the time would have been difficult to identify, and this would have complicated analysis. The questions on brand allowed categorisation of tar, nicotine, and, for some years, carbon monoxide levels. A separate question on time of switching from smoking mainly plain to mainly filter cigarettes was included. Other aspects of smoking were also investigated as well as a whole range of possible confounding variables.

Final discharge diagnoses were subsequently abstracted from the hospital records for 11 847 (93%) of the patients interviewed by HAA clerks or by more senior records staff after the HAA record had been completed. These diagnoses were used to reallocate cases and controls as necessary. Patients without a final diagnosis kept their provisional diagnosis. Patients with multiple index diseases on final diagnosis were classified as lung cancer, if present, and, if not, to the index disease provisionally diagnosed. Overall 1966 (17%) of the patients for whom final diagnoses were available changed their status; 1067 from case to control, 720 from control to case, and 179 from one type of case to another. Where changes had occurred, patients were regrouped into new case control pairs as appropriate.

With the assistance of Sir Richard Doll and Mr Richard Peto, non-index diagnoses were classified as follows:

class 1A "definitely not smoking associated"
class 1B "probably not smoking associated"
class 2A "probably smoking associated"
class 2B "definitely smoking associated"

Controls with no final diagnosis were considered class 1B. At the end of this procedure there were 4950 pairs with class 1 controls and 730 pairs with class 2 controls (table 1).

Interviewing started in the Newcastle locality in 1977 and in Leeds hospitals in 1978 and extended slowly to Manchester, Birmingham, Bristol, East Anglia, South Hampshire, Leicester, Nottingham, and Liverpool, ending in January 1982. Medical staff committees did not grant permission to interview in Oxford and Sheffield. Of 53 hospitals contacted in the 10 regions, seven declined to participate. Within the 46 hospitals, 11 clinicians approached did not wish their patients to be involved. Less than 1% of patients declined to be interviewed, while a few interviews were not completed for various reasons.

The statistical methods used generally followed classical methods for analysis of data from case control studies,[12] cases and controls being separately tabulated by several levels of the risk factor of interest (ie, a 2×K table), with potential confounding factors taken account of by stratification. Results presented are for combined strata and show the (Mantel-Haenszel) relative risk together with the significance of its difference from a base level (risk *1·0*) and/or of the dose related trend. Analysis was generally restricted to comparison of cases with their matched class 1 controls. Analysis also generally excluded the five pairs with ages outside the range initially specified (see table 1).

Results

VALIDITY OF THE DATA

Early on at each location patients were reinterviewed to check the quality of work of the interviewers and the reproducibility of the answers. These 508 second interviews were completed by a more senior

Table 1 *Number of matched pairs after reallocation by class of control*

Sex	Index disease	Class 1 control: Age (yr) 35–54	Class 1 control: Age (yr) 55–74	Class 1 control: All* ages	Class 2 control	Any pair
Male	Lung cancer	375	443	819	206	1025
	Chronic bronchitis	197	340	537	130	667
	IHD	412	399	811	139	950
	Stroke	141	319	460	118	578
	Totals	1125	1501	2627	593	3220
Female	Lung cancer	204	426	630	46	676
	Chronic bronchitis	125	333	460	36	496
	IHD	309	402	712	21	733
	Stroke	126	394	521	34	555
	Totals	764	1555	2323	137	2460

*One male and four female pairs outside age range 35–74.
IHD=ischaemic heart disease.

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interviewer, usually within a few days of the first interview. No significant differences were found for questions having numerical answers. For most questions with qualitative answers, agreement was reached for well over 95% of patients. For the questions on reason for changing smoking habits and on brand smoked 10 years ago, discrepancies occurred in 3·5 to 5% of answers.

The final discharge diagnoses of 1002 patients were independently abstracted by MRA from the clinical records. Comparison with the diagnoses abstracted by the records staff showed no difference for 88%, a minor difference for 10·6%, and a major difference that would have affected allocation of the patients for 1·4%.

All subjects who smoked manufactured cigarettes were asked whether these were filter or plain and, in a separate question, what the brand was. This allowed comparison of filter/plain status as directly asked and as indirectly assessed from the brand. The discrepancy between these two sources of information rose from 2–3% at the time of admission to 8–10% for smoking habits 10 years before admission. The proportion classified as plain smokers was, however, similar from the two sources.

Further validity checks were made by comparing smoking habits of class 1 controls with those seen in population surveys conducted for the Tobacco Research Council (TRC)[13] (table 2). At admission, the hospital controls have a similar proportion who have never smoked, a considerably higher percentage of ex-smokers, and a lower percentage of current smokers of filter cigarettes and of other products (pipe, cigar, handrolled cigarettes). The increase in ex-smokers among hospital controls indicates an appreciable bias.

Among controls who smoked manufactured cigarettes, a markedly higher percentage reported smoking plain cigarettes than expected from TRC national survey data. This was evident not only at admission, but also in earlier years (table 2). Over the whole period the odds of a class 1 control being a plain smoker relative to the TRC national data averages around 1·5 for males and 2·2 for females. This bias is large compared with the estimates of plain/filter relative risk reported in other studies.

Table 2 *Comparison of smoking habits reported by class 1 control patients and by respondents in Tobacco Research Council (TRC) surveys*

Smoking habit	Time	Males		Females	
		TRC	Controls	TRC	Controls
*Percentage of total population**					
Never smoked	At admission	18·2	15·5	44·4	43·2
Ex-smokers	At admission	26·9	40·1	17·9	28·1
Smoker—not man. cigs.	At admission	17·6	11·8	0·8	0·4
Manufactured cigarettes					
Plain	At admission	5·7	7·8	1·9	3·2
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Percentage of all manufactured cigarettes smokers†					
Plain	1979	17·6	25·6	4·8	12·3
Plain	1976	22·3	30·9	7·2	15·0
Plain	1974	29·2	35·6	10·4	19·0
Plain	1969	36·0	48·0	17·2	26·5

*Standardised for age and year of admission.
†Standardised for age and region.

"COMPENSATION"

Smokers who switch to cigarettes with reduced tar and nicotine might in theory "compensate" by increasing numbers of cigarettes smoked or by altering the way they smoked. No evidence of increased consumption was seen in analyses comparing smokers who had or had not decreased the nicotine yield of the brand they smoked between 10 and 5 years before admission. It was not possible to evaluate the second form of compensation.

RELATIVE RISK IN RELATION TO SMOKING

Table 3 presents risks by lifetime history of smoking. In both sexes cigarette smoking was highly significantly associated with lung cancer, chronic bronchitis, and, in the 35–54 age group, ischaemic heart disease. It was not significantly associated with ischaemic heart disease in older subjects or with stroke. Risks of lung cancer and chronic bronchitis were higher, though not significantly, in handrolled than in manufactured cigarette smokers. In the absence of cigarettes, pipe and/or cigar smoking was associated with an increased risk of lung cancer but not of other diseases. Additional analysis showed smoking to be more strongly associated with squamous and small cell lung cancer than with other types of lung cancer.

In table 3, comparisons are based on final diagnosis. Comparison was also made of those whose diagnosis had or had not changed from that provisionally assigned. While some differences in smoking habits were seen, in particular a tendency for control patients originally interviewed as cases to be more often smokers than those originally interviewed as controls, the extent of any potential bias seemed slight (see full report for details).

In both sexes, number of manufactured cigarettes smoked per day at time of heaviest smoking was significantly related to lung cancer, chronic bronchitis, and, in those aged 35–54, ischaemic heart disease. In females, a dose-relation was also seen for ischaemic heart disease in the older age group.

Table 4 presents risks by time manufactured cigarettes were last smoked. Compared with those still smoking at admission, risk of lung cancer was significantly increased among those last smoking one or three years before, presumably because many

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Table 3 *Relative risk (R) of index diseases compared with those who have never smoked by lifetime history of smoking (standardised for age) together with number of cases (N1) and controls (N2)*

			Index diseases				
Sex	*Lifetime history of smoking*		*Lung cancer*	*Chronic bronchitis*	*IHD 35–54*	*IHD 55–74*	*Stroke*
Male	Never smoked	R	1·00	1·00	1·00	1·00	1·00
		N1	15	25	46	51	60
		N2	133	63	77	49	68
	Pipe and/or cigars, no cigarettes	R	3·82++	1·20	0·73	0·83	1·13
		N1	17	8	4	21	23
		N2	35	19	9	23	23
	Pipe and/or cigars and cigarettes	R	9·09+++	2·56++	2·42+++	0·83	1·48
		N1	206	113	122	112	112
		N2	179	132	85	120	84
	Handrolled cigarettes only	R	18·05+++	5·74+++	2·56	1·00	1·03
		N1	32	21	12	6	12
		N2	13	9	10	5	13
	Handrolled and manufactured cigarettes	R	12·87+++	3·23+++	2·42++	1·30	1·06
		N1	159	92	58	31	48
		N2	100	66	48	22	50
	Manufactured cigarettes only	R	9·27+++	2·82+++	1·63+	0·91	1·05
		N1	385	276	161	168	201
		N2	349	243	178	175	220
Female	Never smoked	R	1·00	1·00	1·00	1·00	1·00
		N1	75	105	69	156	231
		N2	243	203	119	181	239
	Manufactured cigarettes only	R	4·75+++	2·79+++	2·13+++	1·30	1·10
		N1	530	333	231	232	272
		N2	371	239	184	208	267

NB Women who have ever smoked pipes, cigars or handrolled cigarettes excluded. Controls are class 1.
+++ $p<0{\cdot}001$; ++ $p<0{\cdot}01$; + $p<0{\cdot}05$; compared with never smoked.

Table 4 *Relative risk (R) of index diseases by time last smoked manufactured cigarettes (standardised for age)*

			Index diseases			
Sex	*Time last smoked manufactured cigarettes*		*Lung cancer*	*Chronic bronchitis*	*IHD 35–54*	*IHD 55–74*
Male	At admission	R	1·00	1·00	1·00	1·00
	1 or 3 years before	R	1·81++	1·05	1·27	1·80
	5 or 10 years before	R	0·43−−	0·89	0·68	1·14
	Earlier	R	0·32−−−	0·65	0·50	1·55
	Never smoked	R	0·10−−−	0·33−−−	0·56−	1·37
Female	At admission	R	1·00	1·00	1·00	1·00
	1 or 3 years before	R	2·08+++	0·85	0·84	0·73
	5 or 10 years before	R	0·65	1·01	0·56	0·74
	Earlier	R	0·28−−−	0·51−	(0·41)	0·55−
	Never smoked	R	0·22−−−	0·29−−−	0·41−−−	0·60−−

NB Subjects who have ever smoked pipes, cigars or handrolled cigarettes excluded. Bracketed figure based on less than 10 cases.
+++,−−− $p<0{\cdot}001$; ++,−− $p<0{\cdot}01$; +,− $p<0{\cdot}05$; compared with at admission.

smokers with lung cancer gave up smoking shortly before admission. Risk was significantly decreased among long-term ex-smokers. A similar pattern seemed to be true for chronic bronchitis, except that here sufferers may have given up smoking because of the disease many years before admission. The evidence regarding heart disease is less clear, though long-term ex-smokers and never smokers had similar risks in all analyses. Here, and subsequently, results for stroke are not presented as no clear associations with any aspect of smoking were seen.

Table 5 compares risk in smokers of filter and plain cigarettes. Standardisation takes account of possible confounding by number smoked. The tendency for smokers to change their habits because of disease is taken account of by ignoring recent changes in smoking, comparisons being based on lifetime habits up to three years before admission. In an additional analysis, not shown in detail here, comparisons were made based on filter/plain status at specific time points, 3, 5 or 10 years before admission.

In males, lung cancer was not significantly related to type of cigarette smoked. In females, some reduction in risk was seen in those who had never smoked plain cigarettes, but no trend was evident in relation to length of use of filter cigarettes. Nor did

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Table 5 *Relative risk (R) of index diseases by lifetime filter/plain smoking habits for those smoking manufactured cigarettes 3 years before admission regardless of whether they subsequently gave up (standardised for age and number of cigarettes smoked 3 years before admission) together with number of cases (N1) and controls (N2)*

Sex	Lifetime filter/plain smoking habit*		Index diseases: Lung cancer	Chronic bronchitis	IHD 35–54	IHD 55–74
Male	Always plain	R	1·00	1·00	1·00	1·00
		N1	105	70	22	23
		N2	73	36	33	42
	Switched to filter up to 10 years before admission	R	1·13	0·80	2·96+	2·02
		N1	47	36	21	16
		N2	28	22	10	14
	Switched to filter more than 10 years before admission	R	1·09	0·43−−	1·69	1·68
		N1	135	49	65	42
		N2	88	64	57	44
	Always filter	R	1·48	0·25−−	1·78	2·67
		N1	35	8	19	11
		N2	24	16	19	7
	Ever filter/never filter	R	1·20	0·50−−	1·83	1·90
	Never plain/ever plain	R	1·48	0·45	1·05	1·85
Female	Always plain	R	1·00	1·00	1·00	1·00
		N1	62	33	23	21
		N2	37	23	4	21
	Switched to filter up to 10 years before admission	R	1·04	1·47	0·18−	1·02
		N1	44	30	17	22
		N2	23	14	23	14
	Switched to filter more than 10 years before admission	R	1·41	1·16	0·39	1·55
		N1	170	85	85	52
		N2	69	40	54	36
	Always filter	R	0·85	0·75	0·24−	1·32
		N1	134	63	73	51
		N2	100	63	61	43
	Ever filter/never filter	R	1·09	1·04	0·27−	1·41
	Never plain/ever plain	R	0·66−	0·64	0·77	0·98

*Smoking habits less than 3 years before admission in which interview occurred ignored so that always plain and never filter include some subjects who switched to filter in this period.
NB Subjects who have ever smoked pipes, cigars or handrolled cigarettes excluded.
+++,−−− $p<0.001$; ++,−− $p<0.01$; +,− $p<0.05$.

female lung cancer risk vary by filter/plain status at any given time point.

In males, there was a clear reducing trend in chronic bronchitis risk by time of switch. In females, no significant differences were seen though, as for lung cancer, those who had never smoked plain cigarettes had the lowest risk.

The results for ischaemic heart disease showed evidence of conflicting patterns with an advantage to filter cigarette smokers for females and a disadvantage for males. However, no filter/plain differences were seen in either sex when subjects were classified according to smoking habits 10 years before admission.

In an attempt to exclude patients who had altered their smoking habits because of onset of symptoms, analyses were carried out for lung cancer on patients who had not been previously hospitalised and who did not have symptoms of chronic bronchitis. This markedly reduced the number of patients available. The general relation of increased risk to heavy smoking was evident, but no significant reduction in risk in smokers of filter cigarettes was seen.

In table 5, patients who had ever smoked products other than manufactured cigarettes were excluded. In additional analyses, smokers of manufactured cigarettes and other products who had ever smoked filter cigarettes had less than half the risk of lung cancer of those who had never smoked filter cigarettes ($R=0.45$, $p<0.01$). Analyses of all manufactured cigarette smokers and of only those who also smoked other products were also carried out for men for the other diseases, but conclusions were unaffected.

Subjects were categorised by the tar level of the brand of cigarettes smoked 10 years before admission. Though the lowest tar group generally had the lowest risk, the differences within any diagnosis were not marked or very consistent between the sexes, the only analysis showing a significant ($p<0.05$) trend being for chronic bronchitis in males, where the risk was almost twice

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as high in smokers of brands with tar yields of 29+ mg as in smokers of brands with tar yields of 17–22 mg.

For lung cancer and ischaemic heart disease, change in number of cigarettes smoked was not related to risk. Risk of chronic bronchitis was higher in those who had recently reduced the number of cigarettes smoked.

No clear relation of inhalation, relighting, tar/nicotine ratio, holding the cigarette in the mouth or butt length to risk of the index diseases was seen; nor were conclusions affected by taking into account any of the wide range of potential confounding variables studied. Details of these and many other analyses carried out are given in the full report.

Discussion

Before attempting to interpret the results, one must consider the validity of the data collected and the possibility of faults in the study design. Considering validity first, it seems from such independent checks as are possible that the data are of the level of accuracy usually obtained in large epidemiological studies. That control patients originally interviewed as cases were somewhat more likely to be smokers than those originally interviewed as controls is consistent with some degree of bias due to patients or interviewers being aware of the diagnosis but may be due to knowledge of smoking habits affecting preliminary diagnosis. More serious are doubts about the validity of the smoking history data; about 10% of the subjects said that they smoked a brand 10 years before admission that was inconsistent with answers to a previous question on the time of switch from plain to filter cigarettes.

It is clear that our control patients, even though not suffering from smoking related diseases, contained relatively more ex-smokers than expected from the general population. Also, the proportion of cigarette smokers reporting smoking plain cigarettes was higher than is seen nationally, not only at admission, but also for the whole 10 years before admission. Whether the factors leading to this discrepancy have also applied to cases is not clear, and this creates difficulty in interpreting the results of the analyses of switching to filter cigarettes. It is not, however, self-evident that comparison with population controls would automatically produce the correct results. This query over the ratio of plain to filter cigarette smokers among the controls has an important bearing on the interpretation of the results for which there is no known correction.

In theory, those who switch to cigarettes with reduced tar and nicotine may "compensate" by either increasing the number of cigarettes smoked daily or by altering the manner of smoking. A number of studies have indicated that compensation by increasing cigarette consumption is, at most, only minimal,[14] and our failure to find any evidence of such an effect confirms this impression. In the present study, it was not possible to check whether the way of smoking had altered intake of tar or nicotine.

Another problem in relating risk to type of cigarette smoked is that there is no time when there are substantial numbers of both smokers of the old high tar plain cigarettes and of smokers of the reduced tar filter cigarettes.

A final problem general to case control studies lies in doubts about their ability to detect other than substantial differences in risk. The method has recently been the subject of considerable criticism.[15] Biases in many such studies may distort the relative risks recorded, while small numbers and errors in the data can reduce the power to detect a real effect. As a rule-of-thumb it is suggested that a well designed case control study should be able to confirm a twofold difference in risk but that, for differences less than this, the power of the study design may be inadequate.

As many have found, the risk of lung cancer, chronic bronchitis, and, particularly in those aged 35–54, ischaemic heart disease was positively associated with the number of manufactured cigarettes smoked daily and was negatively associated with long-term giving up. A number of pieces of evidence suggested that those with an increasing burden of disease are likely to give up smoking or reduce the number of cigarettes they smoke. These include the increased risk in recent ex-smokers of lung cancer (in both sexes) and of ischaemic heart disease (in males), the lack of dependence of risk of chronic bronchitis on whether or not a smoker gave up smoking up to 10 years before admission, and the tendency for risk of chronic bronchitis to be higher for those who reduce the number of cigarettes they smoke than for those who do not.

A review[16] of the effect of type of cigarette on risk of disease emphasised the consistency of the results, despite the diverse nature of the reported studies, noting that generally smokers of filter (or lower tar-nicotine) cigarettes have a lower mortality than smokers of plain (or higher tar-nicotine) cigarettes for those diseases most strongly associated with smoking, and a slightly reduced mortality for those diseases less associated with smoking. It is of interest to compare and contrast findings from the present study and from other studies for each of the four index diagnoses in turn.

For lung cancer, findings from 11 studies[1–5 7–11 17] provide 20 separate results. Nineteen show a reduced

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risk in filter or lower tar cigarette smokers, the weighted average relative risk being 0·71 for males and 0·60 for females. In the current study, no evidence of a reduction in risk in relation to filters was seen in male smokers of manufactured cigarettes only, but some evidence of a reduction in risk was seen for those who had never smoked plain cigarettes compared with those who had ever smoked plain cigarettes *(a)* in females (relative risk = 0·68) and *(b)* among males who also smoked other products (relative risk = 0·57). For females, however, because the highest risks were seen, not in lifetime plain cigarette smokers but in smokers who had switched from plain to filter over 10 years before admission, other comparisons of risk in filter and plain smokers did not show any advantage to filters.

In comparing our results with those of other studies, a number of points have to be considered. Firstly, some variation is to be expected due to sampling error with 95% confidence limits of the relative risk for most comparisons at least ±30%. Secondly, there is the question of how to take into account the smoking of products other than manufactured cigarettes. As we did, Dean[2] excluded such smokers to avoid problems of adequate standardisation particularly of number of handrolled cigarettes and to give a "cleaner" sample, but many studies have included such smokers. Thirdly, we have shown that the ratio of plain to filter cigarette smokers is much higher in the hospital controls than is seen nationally; it is unreasonable to assume that this is a problem specific to our study, but other studies do not appear to have carried out this check. For example, Lubin[7] presented tables demonstrating that a substantial proportion of "lifetime filter smokers" had smoked filter cigarettes for over 40 years, no comment being made that sales of filter cigarettes were extremely low even 30 years ago.[14]

Such data as are available for chronic bronchitis or emphysema from other studies all show an advantage to filters or reduced tar-nicotine (T-N). Thus Dean[2] found significantly reduced risks in filter cigarette smokers in both men and women while Hammond[16] found non-significantly reduced risks, compared with high T-N smokers, in both medium and low T-N smokers. The clear reduction seen in our study in filter cigarette smokers in males, coupled with the somewhat lower risks seen in females who have never smoked plain cigarettes, seem not inconsistent with this evidence. However, it should be remembered that analysis of the effect of type of cigarette on chronic bronchitis is particularly difficult, especially in case control studies, because of the undoubted tendency for sufferers to change their smoking habits because of the disease.

Six studies for ischaemic heart disease[2 3 5 6 17 18] provide 11 sets of comparisons. Although three show some apparent adverse effect of the switch to filters or reduced nicotine cigarettes, none is statistically significant. Indeed, apart from the large Hammond study, where significant reductions in risk of 10–20% were seen in three of the four analyses, all other results have quite wide confidence limits and are consistent with the weighted average relative risk of 0·96 for males and 0·85 for females for all the studies combined. Our results, if reported smoking habits 10 years before admission are considered, are also not inconsistent with this weighted average. However, if one considers analyses based on smoking habits closer to admission, the patterns are much less clear and are conflicting for the two sexes. Thus, compared with smokers who always smoke plain cigarettes, those switching to filters in the 10 years before admission show a risk of ischaemic heart disease that is significantly increased in men, significantly decreased in women aged 35–54, and unchanged in women aged 55–74. An explanation for these conflicting patterns is not easy but may lie partly in the effect of incipient disease on smoking habits and partly in the inaccuracy of statements regarding smoking habits.

Whether smoking itself is related to the incidence of stroke is not established. Both Dean[2] and Hammond[16] show lower risks in filter or reduced T–N smokers, though only in one analysis (Hammond : male : low *v* high T-N) was the reduction statistically significant. Our own study found no significant relation of either lifetime smoking history or type of cigarette smoked to stroke.

Our results do not show, for any of the four diseases, an advantage to filter cigarettes that is clearly evident in both sexes. However, they are compatible with the general impression from other studies that switching to filter cigarettes is likely to show a benefit for lung cancer and for chronic bronchitis. In trying to find reasons for the unclear result, a number of points should be made. (1) There is clear evidence of a bias from patients with incipient disease (whatever the cause) altering their smoking habits. (2) Smokers are now more inclined to accept that smoking entails risks of respiratory disease and heart disease than hitherto.[19] This may have affected the validity of the responses to the questions on smoking. (3) Filter and plain cigarettes differ from country to country, and from time to time with consequent variation in relative risk. (4) Those who initially switched to filter cigarettes may have been individuals who obtained a lower intake per cigarette by virtue of the way they smoked (thus being at lower risk of disease independently of their switch to filter

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cigarettes). (5) Individuals switching to filter cigarettes may "compensate" to some extent for the reduced deliveries of smoke constituents by adjusting the way in which they smoke.[14] These five points taken together may help to explain differences between our results and those seen in other studies, though one cannot quantify their relative importance.

Those concerned to reduce the burden of disease from smoking will wish to consider the present results. The data confirm that never smoking is the ideal, with starting smoking "late", keeping the maximum number of cigarettes down to a low level, and stopping smoking "early" all associated with a reduced risk. The results also indicate, in line with those of other studies, that, at least for lung cancer and chronic bronchitis, switching to filter cigarettes may be associated with lower risks of these diseases. Our findings, especially for lung cancer, are not particularly clear, and the study highlights a number of difficulties in obtaining valid estimates of the effects of changing the type of cigarette smoked. More research is needed. This is in agreement with a recent statement that evaluation of the health effects of low yield cigarettes will remain a challenge to experimentalists and epidemiologists for many years to come.[20]

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Data on tar, nicotine, and CO yields of brands were provided by the Tobacco Advisory Council and by Professor Nicholas Wald, when not available in published statistics.

Any views expressed in this paper are those of the authors and not of any other person or company.

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FAGLIGT OG SOCIALT

Lungecancer og cigarettjære i Danmark

Af **Anne Prener & Ole Møller Jensen**

Der anmeldes årlig ca. 2.800 nye lungekræfttilfælde til Cancerregisteret, og lungecancer er i dag i Danmark den hyppigste cancerform hos mænd og den fjerdehyppigste hos kvinder. I årene 1978-1980 udgjorde lungecancer 18% af alle maligne tumorer hos mænd (1), og denne cancerform var i 1980 årsag til 7% af alle dødsfald blandt mænd (2). Der er siden 2. verdenskrig sket en eksplosiv stigning i lungecancerincidensen, først hos mænd og siden hos kvinder, og lungecancer antages at være den hyppigste kræftsygdom blandt mænd på jorden (3).

Tobaksrygningens betydning, her specielt cigaretrygning, som årsagsfaktor til lungecancer har været kendt i mere end 30 år (4, 5). Selv om der er holdepunkt for, at en række arbejdsmiljøpåvirkninger og luftforurening er af betydning for lungecancerudviklingen (6, 7), er intet enkelt forhold i dag af så stor betydning som cigaretrygning, der skønnes at være den dominerende risikofaktor for 80-90% af alle lungecancertilfælde. En ekspertgruppe under *International Agency for Research on Cancer* har for nylig angivet, at der er tilstrækkelig evidens for, at tobaksrøg er kræftfremkaldende hos mennesker. Tobaksrøgens karcinogene egenskaber afhænger ifølge ekspertgruppen af cigaretternes tjæreindhold (i flere sammenhænge kan udtrykket kondensat ses benyttet, dette dækker over det samme begreb som tjære), og et fald i lungecancerincidensen i England og Wales er kædet sammen med indførelsen af »*low tar*« cigaretter (8, 9).

Formålet med den foreliggende undersøgelse er at analysere den tidsmæssige udvikling af lungecancer i Danmark i relation til cigaretkonsum og det gennemsnitlige tjæreindhold i cigaretter i et internationalt perspektiv. Interessen er især koncentreret om lungecancerudviklingen i de yngre aldersgrupper, hvor indflydelsen på cancerincidensen af cigaretter med lavt tjæreindhold kan antages at være mest udtalt (9).

Registrering af lungecancerincidens

Incidensen af lungecancer (ICD-8: 162 (10)) i forskellige egne af verden er opført i monografien »Cancer Incidence in Five Continents«, Vol. IV (11), som dækker perioden fra 1973-1977. Alle incidenstal er direkte standardiserede for alder under anvendelse af verdenspopulationen som standard.

Incidensen i Danmark af primær lungecancer og lungetumorer uden angivelse af, om de er primære eller sekundære (ICD-7: 162,1 og 163 (12)), i de enkelte aldersgrupper og geografiske områder fremgår af publikationerne fra Cancerregisteret (1, 13-17).

Den foreliggende undersøgelse omfatter tillige en præliminær opgørelse af incidensen for femåret 1978-1982. For årene 1981 og 1982 mangler registreringen af tumorer, for hvilke oplysninger stammer udelukkende fra dødsattester. Dette har hidtil svaret til 5-10% af det totale antal anmeldte tumorer i et kalenderår med relativt flere i de ældre aldersgrupper end i de yngre. En sammenligning med dødsattesterne for de 2 år viser, at denne procentdel kan antages at være uændret for 1981-1982. Da det kun drejer sig om 2 år i en 5 års periode, og da procentdelen af tumorer udelukkende registreret ved dødsattester er væsentligt mindre i de yngre årgange (1968-1972 2-3% for personer under 55 år (16)), er der ikke korrigeret for disse manglende tumorer i den følgende tekst.

CIGARETTER: FORBRUG OG TJÆREINDHOLD

Oplysninger vedrørende cigaretsalget i Danmark stammer for perioden 1920-1938 fra tobaksindustrien (18) og for perioden 1939-1982 fra Danmarks statistik (19). Tallene angiver salg af både indenlandsk producerede cigaretter og importerede cigaretter. Med hensyn til markedsandel for filtercigaretter gælder disse tal udelukkende for cigaretter produceret af Skandinavisk Tobakskompagni, men selskabets totale markedsandel i Danmark er næsten 100%. Oplysninger om toldfri import og forbrug af hjemmerullede cigaretter indgår ikke i de angivne tal. Oplysninger om cigaretsalg og markedsandel for filtercigaretter i England fremgår af LEE's publikationer (20, 21).

De danske tal for tjæreindhold er oplyst fra Skandinavisk Tobakskompagni og er beregnet ud fra cigaretternes røgværdi. Røgværdi bestemmes ved hjælp af en rygemaskine, der ryger 20 cigaretter ad gangen med standardiseret sugefrekvens og volumen samt fast rygelængde. Rygningen foregår gennem et specialfilter, der efter afsluttet rygning indeholder den totale mængde tjære fra cigaretten. Ud fra tjæreindholdet i disse filtre beregnes tjæreindholdet per cigaret. De enkelte værdier for de enkelte cigaretmærker er herefter vægtet efter den pågældende cigarets markeds-

Fra Cancerregisteret, København, Institut for cancer epidemiologi under Kræftens bekæmpelse.

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andel. De oplyste værdier er alle vand- og nikotinfri. Tjæreindhold per cigaret i England er bestemt på tilsvarende vis og ligeledes angivet vand- og nikotinfrit (20).

Lungecancerincidensen i udvalgte lande

International variation. Af Fig. 1 ses det, at den aldersstandardiserede (verdensstandard) lungecancerincidens i midten af 1970'erne hos danske mænd ligger på niveau med incidensen i Canada, Frankrig og Australien. Incidensen er ca. halvdelen af, hvad der kan ses hos Maorierne i New Zealand, og ca. ⅓ af incidensen i England. Finland ligger en del højere end Danmark, mens incidensen i Norge og Sverige ligger på under halvdelen af den danske. For de danske kvinder (Fig. 2) er billedet noget anderledes, idet incidensen her er den højest registrerede blandt kvinder på det europæiske kontinent. Incidensen hos danske kvinder er dobbelt så høj som hos kvinder i de øvrige nordiske lande, men overgås af incidensen i England, Skotland og Nordamerika. Kinesiske kvinder har, ligesom Maori-kvinderne i New Zealand, en høj risiko for lungecancer.

Tidsmæssig udvikling i Danmark. Fig. 3 viser udviklingen i antal af nydiagnosticerede tilfælde af lungecancer per 100.000 henholdsvis mænd og kvinder i perioden 1943 til 1982. Incidensraterne er aldersstandardiserede (verdensstandard) for at eliminere indflydelse fra ændringer i befolkningens aldersmæssige sammensætning. Ses på Danmark under ét, er der i den angivne periode sket en femdobling af lungecancerincidensen for mænd, mens incidensen blandt kvinder næsten er seksdoblet. Lungecancerincidensen hos kvinder er fortsat kun på et niveau, der svarer til, hvad man så hos mændene for ca. 30 år siden. I modsætning til incidensen hos mændene, der i de sidste 10 år har vist en tendens til stabilisering, er stigningen i incidensen fortsat kraftig hos kvinderne, og alene stigningen fra 1973-77 til 1978-82 har været på 28%.

For mændene er incidensudviklingen meget forskellig i de forskellige dele af landet, idet der fortsat ses en stigning i antallet af lungekræfttilfælde blandt københavnske mænd og blandt mænd i landdistrikterne. Stigningen blandt københavnske mænd er dog kun halvt så stor fra 1973-77 til 1978-82 som fra 1968-72 til 1973-77. Blandt mænd i hovedstadens forstæder kan

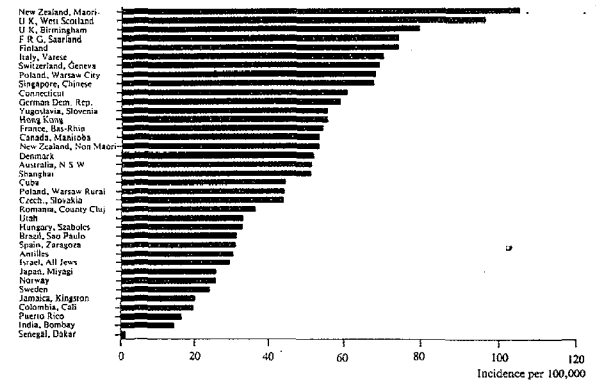

Fig. 1. *International variation in age-standardized lungcancer incidence rates in men around 1975 (World standard population).*

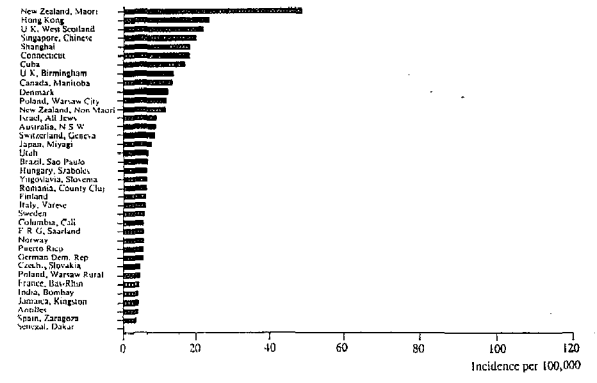

Fig. 2. *International variation in age-standardized lungcancer incidence rates in women (World standard population).*

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iagttages et lille fald inden for de sidste 10 år. Tilsvarende er ikke iagttaget hos kvinderne, hvor der i alle områder ses en kraftig stigning i incidensen med den største stigning i landdistrikterne (43% fra 1973-77 til 1978-82). For kvinder i provinsbyerne er incidensen i perioden fra 1943 til 1982 steget 7½ gang.

Fig. 4 viser udviklingen i incidensen af lungecancer for 5 års aldersgrupper i intervallet 30-54 år separat for de 2 køn og for 4 geografiske områder samt for hele landet. For aldersgrupperne over 45 år ses samme forskel mellem de geografiske områder, som findes for de aldersstandardiserede rater (Fig. 3). Den iagttagne tendens til stabilisering af incidensen for mænd i hele Danmark er til stede i alle de yngre årgange. I aldersklassen 50-54 år, hvor der i perioden fra 1943 til 1968 skete en stigning til mere end det dobbelte, ses der i perioden 1968-72 til 1978-82 kun en lettere stigning.

Det eneste område, hvor der kan iagttages et egentligt fald i lungecancerrisikoen i de yngre årgange, er i de københavnske forstæder, hvor der ses et fald blandt de 30-44 årige. Endvidere ses en stabilisering for de 45-49 årige. Derimod ses en stigning i incidensen i aldersgruppen 50-54 år. For københavnske mænd har antallet af lungekræfttilfælde per 100.000 mænd stort set holdt sig uændret i perioden 1943 til 1982 for de yngste årgange. Derimod ses for 50-54 årige næsten en fordobling i antallet fra 1943 til 1982. I provinsbyerne ses en udfladning af kurverne for alle de yngre årgange, hvorimod der for mænd i landdistrikterne fortsat er en kraftig stigning. Således er risikoen for lungecancer i aldersgruppen 50-54 årige i perioden 1943-82 steget næsten 6 gange.

Blandt kvinderne er billedet helt anderledes, idet der i hele perioden 1943-82 ses en kraftig stigning i alle de yngre aldersgrupper. Stigningen har siden 1950'erne været specielt voldsom, og der er i enkelte aldersgrupper i de sidste 30 år sket en tidobling af risikoen.

Cigaretrygning

Cigaretsalg. Antal solgte, og dermed røgede, cigaretter per indbygger over 15 år ligger i dag i Danmark på ca. 5 per dag. Til sammenligning kan nævnes, at det gennemsnitlige antal per voksen per dag i USA og England er henholdsvis ca. 11 og ca. 8 cigaretter (9). Cigaretforbruget lå i perioden 1920-45 relativt stabilt i Danmark, når man ser bort fra faldet mod krigens slutning (Fig. 5). Udviklingen domineres herefter af en tredobling fra midten af 1940'erne til 1950, som nok til dels kan tilskrives et øget antal rygere blandt kvinder (9). Herefter er der sket en jævn stigning gennem 1950'erne og 1960'erne og i de sidste 10-15 år en tendens til stabilisering på et niveau omkring 5 cigaretter per dag. I England så man mere end en fordobling i cigaretforbruget per voksen per dag i perioden 1920-45. Herefter var der et lille fald fra 1945 til 1950, og siden 1950 har der været en jævn stigning fra ca. 6 cigaretter daglig til ca. 8 cigaretter daglig i 1978.

Foretages en opdeling i filter og ikke-filter cigaretter (Fig. 6), ses det, at filtercigaretter i Danmark har en jævnt stigende markedsandel fra 39% i 1964 til 68% i 1984. Til sammenligning hermed var markedsandelen af filtercigaretter i England i 1981 94%, og allerede i 1967 havde man dér nået en andel på 70% svarende til det nuværende niveau i Danmark.

Tjæreindhold. Det gennemsnitlige tjæreindhold per cigaret i Danmark har igennem de sidste 10 år været jævnt faldende (Fig. 7). Sammenlignes med forholdene i England, ses, at faldet i tjæreindhold satte ind 10 år senere (1975 mod 1965), og at det i Danmark har været mindre markant. I forhold til niveauet i 1964-68 ligger det gennemsnitlige tjæreindhold i Danmark i 1984 8% lavere, mens tjæreindholdet i England er halveret fra 1965 til 1981. Fig. 8 viser markante fald i tjæreindholdet i USA, England, Østrig, Vesttyskland, Schweiz, Australien, Sverige, Norge og Finland sammenlignet med udviklingen i Danmark (21-24). Således ligger tjæreindholdet per cigaret i Danmark i 1984 væsentligt højere end niveauet i de ovennævnte lande i begyndelsen og midten af 1970'erne.

DISKUSSION

I international sammenhæng ligger lungecancerincidensen i Danmark middelhøjt blandt mænd og relativt højere hos kvinder (Fig. 1 og 2), der har den højeste kendte lungecancerrisiko blandt kvinder på det europæiske fastland.

Lungecancerrisikoen i Danmark er fortsat stigende. Dette gælder specielt for kvinder, hvor stigningen de sidste 10 år nærmest har været eksplosiv, mens incidensen hos mænd har vist en stabiliserende tendens (Fig. 3), der er tydeligst i de københavnske forstæder og i de yngre årgange (Fig. 4). Incidensen hos kvinderne er fortsat under ⅓ af, hvad incidensen er hos mændene, men såfremt den voldsomme stigning fortsætter, vil kvinderne nå et niveau svarende til mændenes i løbet af 15-20 år.

I modsætning til denne fortsatte stigning i Danmark har man i England og Wales allerede fra 1950'erne iagttaget et fald i lungecancerincidensen blandt mænd i de yngste aldersgrupper (9). Dette stadige fald betyder, at incidensen i dag er ca. halvdelen af, hvad den var i 1950. Igennem 1960'erne og 1970'erne har faldet bredt sig til også at omfatte årgange op til 60-64 år. I Finland

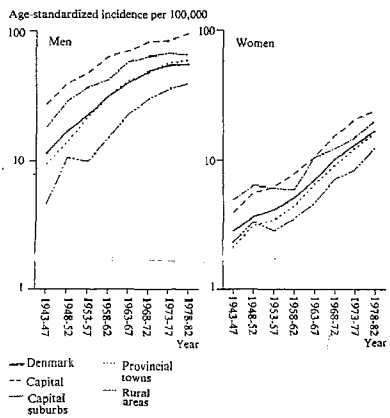

Fig. 3. *Age-standardized incidence (World standard population) of lungcancer in Danish men and women, 1943-1982.*

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og USA har man ligeledes i de sidste år iagttaget fald i incidensen blandt yngre årgange (40-44 år), mens der fortsat ikke ses fald i incidensen blandt de 50-64 årige (9).

Det er som tidligere nævnt en fastslået kendsgerning, at rygning og lungecancerrisiko er tæt årsagsmæssigt associeret (4, 5). De væsentligste komponenter i beviset for denne sammenhæng er, at rygere har en stigende risiko med stigende tobaksforbrug, at 60-årige, der 10 år tidligere har opgivet rygning, har lungecancerrisici, der er ca. halvdelen af 60-årige, der fortsat ryger (9), og at personer, der har skiftet til filtercigaretter med lavere tjæreindhold, har lavere lungecancerrisiko per cigaret (25).

I betragtning af cigaretrygningens dominerende ætiologiske rolle for lungecancer har det været naturligt at søge årsagen til de iagttagne fald i lungecancerincidensen i de nævnte lande i ændringer i rygevanerne de

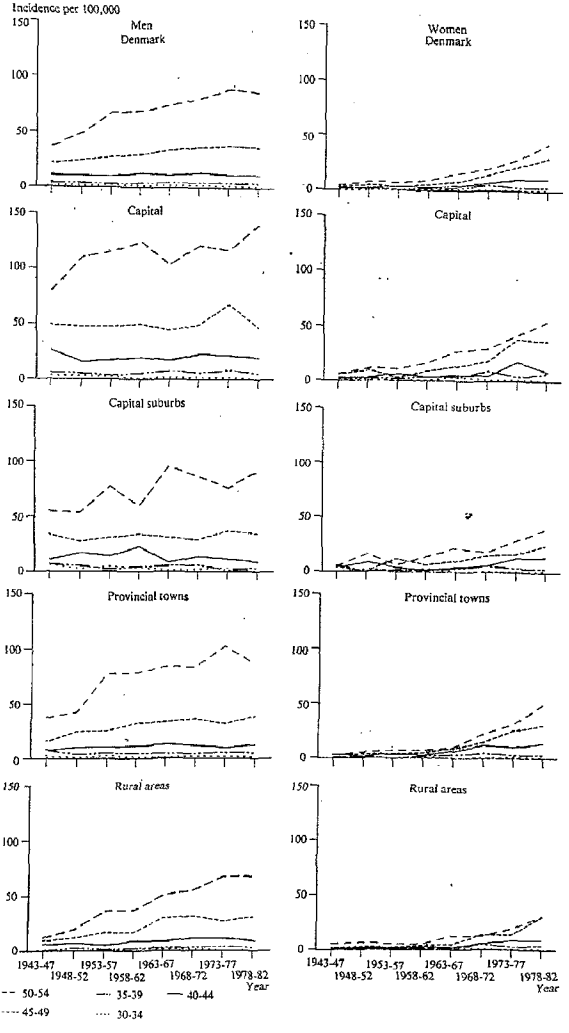

Fig. 4. *Trends in age-specific incidence rates of lungcancer in Danish men and women, age 30-54 years, 1943-1982.*

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sidste 30 år og i forskelle i tjæreindholdet per cigaret. Som anført af DOLL & PETO (9) er der i England siden 1950'erne udført et »naturligt eksperiment« med hensyn til tjæreindholdets betydning for lungecancerincidensen, idet tobaksforbruget per mand siden 1950'erne har været stabilt (den i Fig. 5 viste stigning fra 1950 til 1975 tilskrives udelukkende et øget antal rygere blandt kvinderne (9)). Samtidig er tjæreindholdet per cigaret faldet fra 31,4 mg i 1965 til 15,8 mg i 1981 (21). Den gennemsnitlige tjæreindtagelse per mand er derfor faldet jævnt siden 1950'erne, idet den gennemsnitlige totale mængde indtaget tjære per ryger vil være mindre *ved lavere tjæreindhold* per cigaret. En vis kompensation i form af øget cigaretforbrug og kraftigere inhalering vil finde sted ved skift til cigaretter med lavere tjæreindhold. Denne kompensation opvejer dog ikke faldet i tjæreindhold, og slutresultatet bliver således et fald i tjæreindtagelsen (21). Årsagen til, at incidensfaldet først er iagttaget i de yngre aldersgrupper, skal nok søges i det faktum, at disse aldersgrupper ikke er belastet af forbrug af højkondensatcigaretter (9) som unge i modsætning til de ældre, der i 1930'erne har røget cigaretter med kondensatværdier omkring 35 mg per cigaret (22).

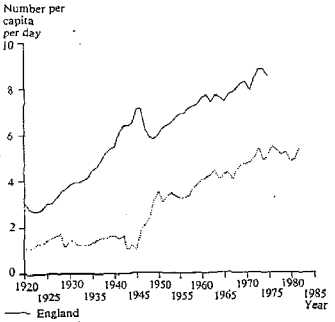


Fig. 5. *Daily per capita (15 years +) consumption of manufactured cigarettes in Denmark and England.*

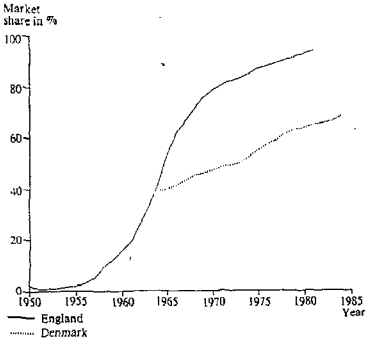


Fig. 6. *Market-share of filter-cigarettes in Denmark and England.*

Cigaretrøg er et kemisk komplekst produkt dannet ved den ufuldstændige forbrænding af tobak. Den præcise kemiske sammensætning af cigaretrøg afhænger af arten af tobak, papirfiltrationen og måden, der ryges på (26). På trods af mange studier kendes den eksakte karcinogene komponent fortsat ikke, men det vides i dag, at de polycykliske aromatiske hydrokarboner (PAH) i røgen er tumorinitiatorer. PAH, som er *kendte karcinogener* (27, 28), er ligesom en lang række andre kemiske forbindelser indeholdt i tjæredelen af røgen.

Andre årsagsfaktorer til lungecancer såsom luftforurening og erhvervspositioner har ligeledes ændret sig i den omtalte periode. Da antallet af lungecancertilfælde, der skyldes rygning, er væsentligt større end antallet af lungecancertilfælde fremkaldt af luftforurening og erhvervspositioner (6, 7), er det overvejende sandsynligt, at det iagttagne fald i lungecancerincidensen blandt mænd i England skyldes faldet i tjæreindtagelse.

Cigaretsalget i Danmark er ikke steget siden ca. 1970. Samtidig er antallet af rygere blandt mænd faldet lidt, fra 41% i 1975 til 39% i 1983, hvorimod rygerprocenten hos kvinderne er steget tilsvarende. Det gennemsnitlige

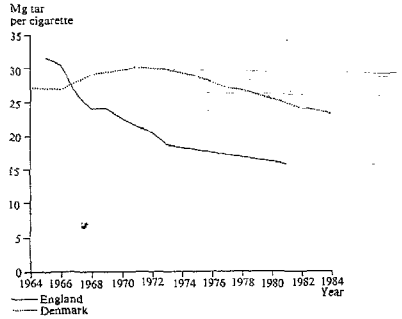
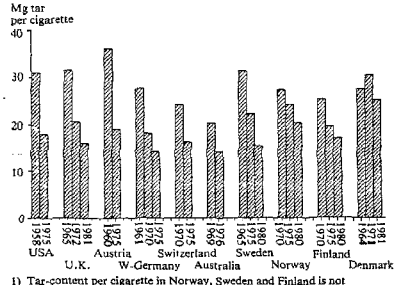


Fig. 7. *Changes in tar-content per cigarette in England since 1965 and in Denmark since 1964.*



1) Tar-content per cigarette in Norway, Sweden and Finland is not nicotinefree. To allow comparison with the other countries the figures should be reduced by approximately 8%.
2) Mean tobacco weight per cigarette shows some variation between the countries, but not enough to account for the differences in tar-content per cigarette.

Fig. 8. *Changes in tar-content per cigarette in different countries (From: 21, 22, 23, 24).*

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fald i cigaretternes tjæreindhold er kun beskedent, og faldet er sat ind relativt sent sammenlignet med andre lande, Fig. 7 og 8. Det kan på baggrund af dette ikke forbavse, at der i Danmark kun ses en stabilisering i lungecancerrisikoen hos mænd i modsætning til de beskrevne fald i flere andre vestlige lande.

Totalt set er tjæreindholdet per cigaret faldet i de fleste lande i verden (Fig. 8) (22). Forskellige former for pression er skyld i disse fald. I visse lande har regeringen på grund af medejerskab tilstrækkelig kontrol med tobaksindustrien til at kunne dirigere udviklingen i retning af nedsættelse af tjæreindholdet. I USA, Canada og Australien har oplysningskampagner ført til en øget bevidsthed hos rygerne om betydningen af tjæreindhold i relation til lungecancer. I USA har konkurrencen om markedet for »*low tar*« cigaretter endvidere bevirket øget opreklamering af disse cigaretmærker, og dette har bidraget til et fald i den gennemsnitlige tjæreindtagelse (22). I modsætning hertil findes i Danmark ingen restriktioner eller målrettede oplysningskampagner vedrørende tjæreindhold i cigaretter. Faldet i tjæreindhold skyldes udelukkende en frivillig indsats fra cigaretproducenternes side. Resultatet af denne indsats svarer ikke til, hvad der i andre lande er opnået ved hjælp af lovgivning, idet Danmark i dag internationalt set ligger i toppen med hensyn til tjæreindhold (21).

RESUMÉ

Ud fra Cancerregisterets statistiske oplysninger for perioden 1943-1977 samt en præliminær opgørelse for perioden 1978-82 er foretaget en analyse af den tidsmæssige udvikling af lungecancer i Danmark i relation til cigaretkonsum og det gennemsnitlige tjæreindhold i cigaretter. Danmark ligger internationalt set meget højt med hensyn til tjæreindhold per cigaret og har samtidig et stabiliserende cigaretforbrug, dog med let stigende antal rygere blandt kvinderne.

I en række vestlige lande, bl.a. England, er der siden 1950 set en faldende lungecancerincidens blandt mænd, hvilket er tilskrevet et faldende gennemsnitligt tjæreindhold per cigaret. I Danmark er lungecancerrisikoen fortsat stigende blandt kvinder, mens incidensen blandt mændene har vist en stabiliserende tendens, der er tydeligst i de københavnske forstæder og i de yngre årgange. Der er således ikke i Danmark iagttaget noget egentligt fald i lungecancerincidensen, hvilket er i overensstemmelse med det uændret høje tjæreindhold per cigaret i Danmark.

Sekretærerne VIVI CLEMMENSEN og MARIANNE HARNEK takkes for renskrivning af manuskriptet. Assistent AASE LARSEN takkes for assistance ved tegning af figurer.

SUMMARY

Anne Prener & Ole Møller Jensen: Cancer of the lung and cigarette tar in Denmark.

Ugeskr Læger 1985; 147; 4221-7.

On the basis of statistical information from the Danish Cancer Registry for the period 1943-1977, and a preliminary review from the period 1978-82, an analysis is undertaken of the temporal development of cancer of the lung in Denmark in relation to the cigarette consumption and the average tar content in the cigarettes. The tar content of cigarettes in Denmark is high as compared with other countries. Simultaneously, the cigarette consumption is stabilized, although a slightly increasing number of smokers among women is observed.

In a number of western countries including Britain, the incidences of cancer of the lung have been observed to decrease since 1950. This is attributed to the decreasing average tar content per cigarette. In Denmark, the risk for development of cancer of the lung is still increasing in women while the incidence in men has shown a stabilizing tendency which is most marked in the suburbs of Copenhagen and the younger age-groups. Thus, no actual fall in the incidence of cancer of the lung has been observed in Denmark and this is in agreement with the unchanged high tar content per cigarette in Denmark.

Send reprint requests to ANNE PRENER, Cancerregisteret, Landskronagade 66, DK-2100 København Ø.

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Original meddelelse

Børnemishandling og omsorgssvigt

Børn af stofmisbrugende forældre

Af **Joav Merrick & Lars Pedersen-Bjergaard**

Stofmisbrug blandt unge har inden for de sidste 10-15 år været et stort problem. Det skønnes (1, 2), at der er 6.000-10.000 stofmisbrugere i Danmark, hvoraf 3.000-5.000 befinder sig i det storkøbenhavnske område. Fra kontakten til behandlingsinstitutionerne (2) ved man, at ⅔ af stofmisbrugerne er mænd og ⅓ kvinder. Gennemsnitsalderen har i de senere år været stigende og er nu for mændenes vedkommende 27-28 år, mens den for kvindens vedkommende er noget lavere.

Stofmisbrugende familier med børn er siden 1975 blevet et problem for social- og sundhedssektoren, idet der er sket en kraftig stigning i antallet af gravide stofmisbrugere (3). I 1975 blev der for hele Danmark registreret omkring 25 børn af stofmisbrugere, men nu fødes der årligt i København omkring 30 børn af stofmisbrugere.

Den gravide stofmisbruger lever et risikofyldt og uregelmæssigt liv (3-7), der bringer fostret og senere det fødte barn i fare for alvorligt omsorgssvigt. Familierne flytter meget, børnene og forældrene er ofte mange gange og langvarigt hospitalsindlagte, kontakten til social- og sundhedssektoren sporadisk og præget af mistillid, og samtidig opnår børnene ikke en stabil opvækst med få voksenkontakter, men derimod mange skift og tilfældige voksenkontakter.

Børnene overlades ofte til sig selv, hos familie, venner eller tilfældige bekendte, hvilket ikke er betryggende og i yderste konsekvens kan medføre, at børnene dør på grund af omsorgssvigt (8).

Formålet med denne undersøgelse har været at vurdere forekomsten, omstændighederne og formen for omsorgssvigt blandt en gruppe børn af stofmisbrugende forældre. Børnene har været i kontakt med et børnehospital i en storby, hvorfor det også har været hensigten at høste viden og erfaring ved denne evaluering til brug for en øget forebyggende indsats i en storby.

EGNE UNDERSØGELSER

Materiale og metode

Materialet (5) består af børn, der i perioden 1975-83 har været i kontakt med Børnehospitalet på Fuglebakken, hvor en af forældrene havde et stofmisbrug. Materialet omfatter 50 børn, men herværende undersøgelse vil kun beskæftige sig med de 17 børn, for hvem vi ud fra journalmaterialet har vurderet, at barnet har været udsat for omsorgssvigt under opvæksten.

Undersøgelsen er retrospektiv, og samtlige journaler er gennemgået af forfatterne og kodet efter et ensartet

Fra Børnehospitalet på Fuglebakken, København.

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Determinants of Lung Cancer Risk in Cigarette Smokers in New Mexico [1,2]

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ABSTRACT—Although cigarette smoking is the strongest known risk factor for lung cancer, the effects of specific smoking practices have not been completely characterized. The present study examines determinants of lung cancer risk in a population-based, case-control study conducted in New Mexico, 1980–82. The study included 521 cases and 769 controls matched for age, sex, and ethnicity. Either the index subjects or their next-of-kin were interviewed in person to obtain a detailed history of cigarette smoking and information concerning other risk factors. With the use of multiple logistic regression, a model was constructed of the effects of amount smoked, duration of smoking, cigarette type, and smoking cessation on lung cancer risk. Among current smokers, risk increased with each additional cigarette smoked per day ($P<.001$). For duration of smoking, the risk per year smoked in individuals 65 years and older was only one-third that in persons under age 65 years. With regard to cigarette type, a somewhat higher risk was found associated with smoking nonfilter cigarettes, but there was no evidence of decreasing risk as the extent of filter smoking increased. Lifelong filter cigarette smokers and smokers of both filter and nonfilter cigarettes were at lower risk than lifelong smokers of nonfilter cigarettes only. In ex-smokers, the pattern of variation of relative risk with amount and duration was similar to that in the current smokers. Excluding those who had stopped for 1 year or less, the relative risk declined exponentially with duration of smoking cessation ($P<.01$). These analyses confirm the strong benefits of smoking cessation and indicate possible reduction of risk from smoking filter cigarettes.—JNCI 1986; 76:597–604.

Laboratory and epidemiologic evidence has established a causal association between cigarette smoking and lung cancer (*1, 2*). In the United States, the majority of lung cancers in men and women can be readily attributed to tobacco smoking (*2, 3*). In spite of intensive investigation, important issues related to the association between lung cancer and cigarette smoking are still unresolved (*4*). While dose-response relationships with intensity of cigarette consumption have been demonstrated, other determinants of risk for lung cancer in smokers remain largely unknown. Commercial cigarettes have continuously evolved through the addition of filters and other modifications designed to reduce tar and nicotine yields (*4, 5*). Reduced risks would be anticipated for low-yield cigarettes; however, methodologic barriers constrain epidemiologic investigations of low-yield cigarettes and beneficial consequences of smoking them have not been fully established. In fact, since extensive modification of the cigarette began in the 1950's, it has only recently become possible to investigate smokers with predominant use of the newer products.

In New Mexico, the descriptive epidemiology of lung cancer differs in the State's Hispanic and non-Hispanic whites (*6*). We have conducted a population-based, case-control study of incident lung cancer cases, 1980–82, designed to explain the differing occurrence of lung cancer in these 2 ethnic groups. The study questionnaire assessed lifetime smoking habits, occupational history, residence history, dietary intake of vitamin A, and other risk factors. Results related to ethnicity, vitamin A, and occupation have been reported elsewhere (*7–9*). In this paper, we have used the detailed smoking history to examine dose-response relationships and the effects of consuming different types of cigarettes.

METHODS

Case selection.—The present analyses involve subjects in a population-based, case-control study of lung cancer in New Mexico. The cases were ascertained statewide by the New Mexico Tumor Registry, a participant in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (*10*). The eligibility criteria limited the series to non-Hispanic and Hispanic white State residents, ages 25 through 84 years, with primary lung cancer other than alveolar cell carcinoma, diagnosed between January 1, 1980, and December 31,

ABBREVIATION USED: OR=odds ratio(s).

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1982. All cases in Hispanics and in non-Hispanic whites below age 50 were included. Non-Hispanic whites, 50 years of age and older, were randomly sampled at a fraction of 0.40 for males and 0.50 for females.

This report is based on the 521 cases interviewed as of August 1, 1983. The diagnosis was established by histology, cytology, or autopsy for 96.4% of the cases and in the remainder by clinical evidence. The overall participation rate either by the cases ($n=274$) or by surrogate respondents ($n=247$) was approximately 91%.

Control selection.—The control series was frequency matched to the cases by age, sex, and ethnicity, at an overall ratio of approximately 1.5 controls per case. Two methods of control selection were employed. First, lists of randomly generated residential telephone numbers were screened to identify potential controls. The screening algorithm required at least 6 calls, which covered weekdays, evenings, and weekends. For each household, the age, sex, and ethnicity of all adults were obtained. Individuals in the appropriate strata of age, sex, and ethnicity were then selected for interview, but only one was taken from each household. Of the 2,108 households contacted, a household census was refused by 287 (14.2%). Second, because this method did not efficiently identify controls over age 65 years, we also sampled from a randomly generated list of New Mexico Medicare participants. According to the Health Care Financing Administration, over 97% of the State's population, 65 years of age and older, is included on the organization's roster. The overall participation rate by persons identified through these two approaches was 83%.

Data collection.—Interviews were conducted by bilingual interviewers according to a standardized protocol. With the exception of 35 respondents contacted by telephone and 4 cases interviewed in the hospital, all interviews were conducted in person in the homes of the cases and controls. The questionnaire obtained information concerning residence history, occupational history, family and personal history of respiratory diseases, and diet. A detailed history of cigarette use was collected for individuals who had smoked for 6 months or more. Because cigarette smokers often stop and then resume smoking, a history was obtained for each time period of cigarette use including the years of starting and stopping, the average number of cigarettes smoked per day, and the number of years that hand-rolled, commercial filter, and commercial nonfilter cigarettes were each smoked. A single question was asked about depth of inhalation, which was characterized as: into the mouth only, into the back of the throat, into the top of the lungs, or deep into the lungs.

Data analysis.—For the present analyses, cigarette smokers were defined as individuals who had smoked cigarettes for at least 6 months. Current smokers were using cigarettes at the time of interview or had stopped smoking within 1 year of the interview. Ex-smokers had stopped smoking permanently more than 1 year before the interview.

The smoking history information was used to calculate various indices of exposure to cigarette smoke (table 1). The total duration (V_9-V_{12}, V_{13}) of cigarette smoking was calculated as the sum of the individual periods of use. The average number of cigarettes smoked per day (V_4-V_7, V_8) was the time-weighted average of the number of cigarettes smoked in each period. With regard to the types of cigarettes that were smoked, two sets of variables were created. First, the percentage of the smoking duration that involved filter cigarettes was calculated and used to create 5 indicator variables (V_{16}-V_{20}) and a continuous variable (V_{21}). The second set of variables was the actual number of years that filter and nonfilter cigarettes were smoked (V_{14}, V_{15}). For these analyses, the nonfilter category included hand-rolled and commercial nonfilter cigarettes.

Conventional stratified analysis and multiple logistic modeling were employed. As required by the frequency matching in the study's design, all analyses included appropriate adjustment for age, sex, and ethnicity. For current smokers, we first used the Mantel-Haenszel method to calculate relative risk estimates separately for the effects of amount and duration with adjustment for age (2 strata), sex, and ethnicity (*11, 12*). In this paper, we provide the Mantel-Haenszel age-specific OR and the Mantel extension χ, which tests for linear trend in risk with increasing dose (*12, 13*). For empty cells, 0.5 was added as appropriate (*12, 13*).

To examine further the effects of the various measures of cigarette smoking, we used multiple logistic regression models that were initially developed separately for the current smokers and ex-smokers of cigarettes (*14, 15*). We evaluated effect modification, i.e., whether the level of the one variable modifies the effect of another,

TABLE 1.—*Measures of tobacco smoking used in the analyses*

Variable	Measures
V_1	Current smoker (1 = current; 0 = never)
V_2	Ex-smokers (1 = ex; 0 = current)
V_3	Age (1 = <65 yr old; 0 = ≥65 yr old)
V_4	Amount 1 (1 = 1–15 cigarettes/day; 0 = else)
V_5	Amount 2 (1 = 16–20 cigarettes/day; 0 = else)
V_6	Amount 3 (1 = 21–30 cigarettes/day; 0 = else)
V_7	Amount 4 (1 = ≥31 cigarettes/day; 0 = else)
V_8	No. of cigarettes smoked/day (continuous)
V_9	Duration 1 (1 = 1–29 yr; 0 = else)
V_{10}	Duration 2 (1 = 30–39 yr; 0 = else)
V_{11}	Duration 3 (1 = 40–49 yr; 0 = else)
V_{12}	Duration 4 (1 = ≥50 yr; 0 = else)
V_{13}	Years of smoking (continuous)
V_{14}	Years of filter smoking (continuous)
V_{15}	Years of nonfilter smoking (continuous)
V_{16}	Filter (1 = filter only; 0 = else)
V_{17}	High filter (1 = 67–99% filter; 0 = else)
V_{18}	Medium filter (1 = 34–66% filter; 0 = else)
V_{19}	Low filter (1 = 1–33% filter; 0 = else)
V_{20}	Nonfilter (1 = nonfilter only; 0 = else)
V_{21}	Percent of smoking duration involving filter use (continuous)
V_{22}	Inhale (1 = top of lungs or deep into lungs; 0 = mouth or back of throat)
V_{23}	Years of smoking cessation (continuous)
V_{24}	Pipe (1 = if ever-pipe use; 0 = else)
V_{25}	Cigar (1 = if ever-cigar use; 0 = else)

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TABLE 2.—*Ethnic, sex, and age distribution of cases and controls by cigarette smoking status in a case-control study of lung cancer in New Mexico, 1980-82*

Ethnic group	Sex	Age, yr	Cigarette smoking status					
			Current smoker		Ex-smoker		Never-smoker	
			No. of cases	No. of controls	No. of cases	No. of controls	No. of cases	No. of controls
Non-Hispanic whites	♂	<65	69	54	18	59	1	35
		≥65	74	58	54	99	6	60
	♀	<65	45	35	8	17	2	47
		≥65	34	14	18	19	11	52
Hispanics	♂	<65	24	22	8	18	0	9
		≥65	38	30	17	28	2	21
	♀	<65	12	8	3	7	2	27
		≥65	15	6	4	5	4	34

by adding product terms to the models or by running the models within specific subsets of the subjects. We assessed possible bias introduced by next-of-kin interviews by performing the analyses separately within groups defined by interview type.

Two sets of models were used for the current smokers, depending on the hypotheses that were being tested; in some, never-smokers were the reference category, whereas in others, only current smokers were included. In models including never-smokers, the value of zero was assigned to the amount and duration variables for never-smokers. Because we found strong and statistically significant interaction between age and duration of smoking, their product was included in all models. To evaluate the effect of types of cigarettes smoked, we used two distinct approaches. In the first approach, we added either the continuous or categorical measures of filter cigarette use to the model that included amount and duration. In the second approach, the duration of smoking was replaced by 2 variables: the years of filter use and the years of nonfilter use, which together summed to the total duration. For never-smokers, these variables assumed the value of zero.

Similar models were developed for the ex-smokers, but all models included the duration of smoking cessation. Standard programs of the Statistical Analysis System (SAS) were used for all analyses (*16*).

RESULTS

The analyses were limited to the 469 cases and the 764 controls with complete information on current cigarette smoking status, amount smoked, and duration of cigarette smoking (table 2). Comparison of the excluded 52 cases and 5 controls with the included subjects showed no differences in the ethnic and sex distributions, but the excluded subjects were significantly older and a higher proportion of surrogate interviews had been necessary for them.

Initially, using stratified analysis, we examined the effects of duration and amount of smoking in current smokers. With never-smokers as the reference category, the age-, sex-, and ethnicity-adjusted OR for lung cancer increased significantly with increasing duration (Mantel extension $\chi=13.9$; $P<.001$) and amount smoked daily (Mantel extension $\chi=14.7$; $P<.001$). The slope of the dose-response relationships for effects of amount and the duration of smoking decreased with increasing age. Because the effects of duration were similar for the age categories below age 65 years (*<55*, *55-64*) and those 65 years or older (*65-74*, *75-84*), we stratified at age 65 years for the present analyses (table 3). With the never-smokers as the reference category, significant linear trends in OR with increasing duration of smoking were observed for both age groups. However, the OR for smokers of 30 years' duration or more were strongly affected by age, with much lower values for those 65 years of age and older.

We further restricted the analysis to current smokers to eliminate the effect of rising lung cancer risk with age in the never-smokers (table 4). For those less than 65 years of age, the OR rose with increasing duration (Mantel extension $\chi=4.1$; $P<.001$ and amount of smoking (Mantel extension $\chi=4.8$; $P<.001$). In contrast, for those 65 years of age and above, no significant increase in risk with increasing duration of smoking was observed (Mantel extension $\chi=0.50$; not significant), but the effect of amount of smoking remained statistically significant (Mantel extension $\chi=3.5$; $P<.001$).

For the simultaneous examination of amount and duration of smoking, the indicator variables corresponding to the categories in the stratified analysis were entered into multiple logistic regression models. Separate analyses were performed for the 2 age groups less than 65 years and 65 years or older. For smokers less than 65 years of age, linear dose-response relationships of log odds were observed for amount and duration of smoking. For smokers 65 years or older, the log odds increased significantly with amount but not with duration of smoking.

Because linear trends in log odds were observed in these analyses, in subsequent models the dose measures for amount and duration were the continuous variables V_8 and V_{13}, respectively. The logistic regression coefficients for the amount and duration of smoking effects are presented in table 5 for the different populations of

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TABLE 3.—*Adjusted[a] OR for lung cancer by age, duration of smoking, and number of cigarettes smoked daily in current smokers relative to never-smokers in a case-control study of lung cancer in New Mexico, 1980–82*

Variable	<65 yr old			≥65 yr old		
	No. of cases	No. of controls	OR	No. of cases	No. of controls	OR
Duration of cigarette smoking						
Never smoked	5	118	1.0[b]	23	167	1.0[b]
1–29 yr	13	31	12.9	7	2	22.9
30–39 yr	61	50	37.3	7	8	6.6
40–49 yr	68	36	57.3	36	23	11.7
50–59 yr	8	2	91.4	82	53	16.1
≥60 yr	—	—	—	29	22	11.9
No. of cigarettes daily						
Never smoked	5	118	1.0[b]	23	167	1.0[b]
1–15	17	33	16.2	40	44	8.6
16–20	44	45	27.6	64	43	12.3
21–30	33	22	47.1	22	10	22.9
≥31	56	19	89.3	35	11	24.3

[a] Adjusted for sex and ethnicity.
[b] $P<.001$ for the Mantel extension χ for linear trend.

TABLE 4.—*Adjusted[a] OR for lung cancer by age and duration of smoking in current smokers only in a case-control study of lung cancer in New Mexico, 1980–82*

Duration of cigarette smoking, yr	OR[b] for individuals <65 yr old	OR[b] for individuals ≥65 yr old	OR[c] for individuals ≥65 yr old
1–29	1.0[d]	1.0[e]	1.0[f]
30–39	3.0	0.3	
40–49	4.8	0.6	1.1
50–59	7.9	1.8	1.7
≥60	—	0.4	1.1

[a] Adjusted for sex and ethnicity.
[b] Smokers of 1–29 years' duration as the reference category.
[c] Smokers of 1–39 years' duration as the reference category.
[d] Mantel extension χ for trend = 4.0; $P<.001$.
[e] Mantel extension χ for trend = 0.4; not significant.
[f] Mantel extension χ for trend = 0.3; not significant.

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TABLE 5.—*Logistic regression coefficients for estimation of lung cancer risk associated with amount smoked and duration of smoking in current smokers and ex-smokers in a case-control study for lung cancer in New Mexico, 1980–82*

Models[a]	Logistic regression coefficients for various cigarette smoking groups								
	Current smoker and never-smoker[b]			Current smoker only			Ex-smoker only		
	<65 yr old	≥65 yr old	All ages	<65 yr old	≥65 yr old	All ages	<65 yr old	≥65 yr old	All ages
Amount (V_3), cigarettes/day	0.050[c]	0.054[c]	0.052[c]	0.052[c]	0.053[c]	0.052[c]	0.049[c]	0.016	0.023[c]
Duration (V_{13}), yr	0.071[c]	0.024[c]	0.026[c]	0.087[c]	−0.010	−0.010	0.069[d]	−0.010	−0.008
Age-duration interaction ($V_3 \times V_{13}$)			0.046[c]			0.098[c]			0.069[d]
Years of smoking cessation (V_{23})							−0.068	−0.078[d]	−0.073[c]

[a] All models included appropriate adjustment for age, sex, and ethnicity.
[b] Never-smokers are included with the natural values of 0 yr and 0 cigarettes/day.
[c] $P<.001$.
[d] $P<.05$.

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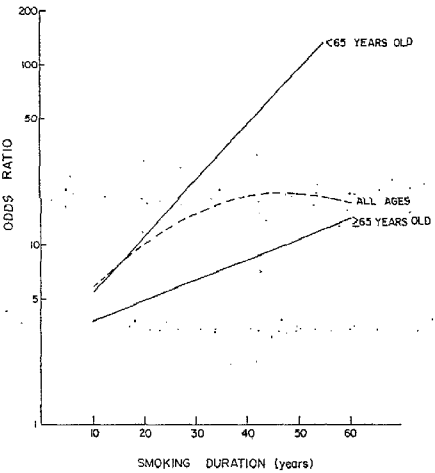
smokers. The logistic coefficient for (V_8) estimates the increase in log odds for each additional cigarette smoked per day. Using the interaction term ($V_3 \times V_8$), we found no effect modification by age for amount. The coefficient for duration (V_{13}) provides the estimate of change in log odds from 1 year of smoking for individuals 65 years of age or older. The coefficient for interaction between age and duration ($V_3 \times V_{13}$) estimates the excess in log odds from 1 year of smoking in those younger than age 65, relative to the older smokers. This interaction term was significant for both current smokers and ex-smokers. Using the logistic coefficients from the model including never-smokers and current smokers, we calculated the OR for a current smoker of given duration, relative to a never-smoker (text-fig. 1). When the interaction variable between age and duration is not included in the model, a significant quadratic effect of duration is observed ($b = -8.6 \times 10^{-4}$; $P < .005$) (text-fig. 1).

The effects of amount and duration of smoking, with adjustment for cessation, were the same for ex-smokers and current smokers (table 5). The lower logistic coefficient for amount smoked in ex-smokers 65 years and older did not differ significantly from the logistic coefficients in the current smokers and younger ex-smokers. We used a combined model for current smokers and ex-smokers to estimate the decline in risk with smoking cessation. The risks in the ex-smokers were compared to those in a current smoker who continued to smoke the same amount while accumulating additional years of smoking duration, in comparison to the smoking duration in ex-smokers. The OR for ex-smokers below age 65 years declined to 0.49, 0.24, and 0.06 for 5, 10, and 20 years of smoking cessation, respectively; for those older than 65 years, the corresponding OR were 0.73, 0.54, and 0.29.

Two approaches were used to evaluate the effect of cigarette type on lung cancer risk in the current smokers. First, we employed indicator variables (V_{16}–V_{20}) or a continuous variable (V_{21}) that represented the proportion of the years of smoking that involved filter cigarettes. Second, we partitioned the duration (V_{13}) into



TEXT-FIGURE 1.—OR for lung cancer, by age group, in current smokers of 20 cigarettes per day, relative to never-smokers (OR for never-smokers=1).

years of filter (V_{14}) and years of nonfilter (V_{15}) use. Because the smoking practices of the Hispanic and non-Hispanic whites differed, we performed the analyses separately for the 2 ethnic groups. At all ages, a higher proportion of Hispanic males and females had ever smoked hand-rolled cigarettes in comparison with the non-Hispanic whites. The differences were more prominent among cases. The average duration of smoking hand-rolled cigarettes was also longer in the Hispanics (table 6). Initial separation of the nonfilter cigarettes into commercial and hand-rolled types showed that generally higher risks were associated with smoking hand-rolled as compared to commercial nonfilter ciga-

TABLE 6.—*Average years of smoking specific types for current smokers who ever used a given type by age, sex, ethnicity, and case-control status in a case-control study of lung cancer in New Mexico, 1980–82*

Sex	Age, yr	Status	Average yr of smoking					
			Hand-rolled cigarettes		Commercial nonfilter cigarettes		Filter cigarettes	
			Non-Hispanic whites	Hispanics	Non-Hispanic whites	Hispanics	Non-Hispanic whites	Hispanics
Male	<65	Case	7.0	18.4	22.5	22.5	20.8	22.7
		Control	7.9	7.1	18.9	13.9	18.1	20.0
	≥65	Case	12.5	24.1	32.8	30.1	19.4	14.2
		Control	9.9	16.0	27.9	27.3	24.5	20.0
Female	<65	Case	4.3	18.3	18.8	21.0	20.5	15.2
		Control	6.0	2.0	15.1	17.2	21.6	15.3
	≥65	Case	9.5	31.7	29.8	30.6	21.4	16.4
		Control	3.0	35.0	29.6	14.3	17.9	25.8

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rettes, but the differences were not significant in any of the age-sex-ethnic strata. Consequently, commercial nonfilter and hand-rolled cigarettes were combined into one nonfilter category.

The effects of filter cigarette smoking differed in the Hispanic and the non-Hispanic whites (table 7). In the Hispanics, the OR declined consistently as the proportion of filter cigarette smoking increased; in the non-Hispanic whites, filter use was associated with lower OR, but a dose-response relationship with the percentage of filter use was not evident. When V_{21} was substituted for V_{16}–V_{20}, there was significant reduction in risk for lung cancer with increased filter use in the Hispanics ($b = -0.024$ per percent; $P<.001$), but not in the non-Hispanic whites ($b = -0.004$ per percent; $P=.30$).

Partitioning the duration into years of filter use and years of nonfilter use showed a similar pattern by ethnic group (table 8). In the non-Hispanic whites, the coefficients for the 2 separate cigarette-type variables were similar. In the Hispanics, nonfilter smoking was associated with a significantly higher risk ($P<.05$). Our conclusions did not change when all individuals who ever smoked hand-rolled cigarettes were eliminated from the analysis.

Because 47% of the case interviews had been with next-of-kin, all the logistic analyses were performed separately within the self-reported and next-of-kin groups. The results for the 2 interview groups were comparable and did not alter our interpretation of the analyses.

The effect of depth of inhalation was evaluated only for current smokers with self-reported data. Smokers who reported inhalation into the top of the lungs or deep into the lungs were at increased risk (OR=2.1; $P<.005$) compared with those who reported inhaling into the mouth or the back of the throat only. We tested for modification of the effect of inhalation by amount smoked; within strata of amount smoked, less than 20 or 20 or more cigarettes daily, the logistic regression coefficients for the indicator variable for inhalation were $b=0.54$ ($P=.18$) and $b=0.80$ ($P<.05$) for the lighter and heavier smoking groups, respectively. When the groups were combined, an interaction term for a differing effect of inhalation with amount smoked was not statistically significant ($P=.40$).

We evaluated the effect of ever-pipe and ever-cigar use by adding variables V_{24} and V_{25} to the models. The logistic regression coefficients for these 2 variables were insignificant, and their values did not indicate important effects on risk.

TABLE 7.—*Ethnic-specific OR for lung cancer in current smokers by the proportion of years that filter cigarettes were used in a case-control study of lung cancer in New Mexico, 1980–82*

Models[a]	OR in:	
	Non-Hispanic whites	Hispanics
Filter only (V_{16})	0.80	0.04[b]
67–99% filter (V_{17})	0.71	0.26[b]
34–66% filter (V_{18})	0.58	0.39
1–33% filter (V_{19})	0.83	0.56
Nonfilter only (V_{20})[c]	1.00	1.00

[a] In addition to age, sex, and ethnic variables, V_8 (amount), V_{15} (duration), and $V_8 \times V_{15}$ (age-duration interaction) were included in the models.
[b] $P<.05$.
[c] Reference category.

TABLE 8.—*Age- and ethnic-specific logistic coefficients for estimation of lung cancer risk associated with duration of filter and nonfilter cigarette use in a case-control study of lung cancer in New Mexico, 1980–82*

Models[a]	Logistic coefficients in:			
	Non-Hispanic whites		Hispanics	
	<65 yr old	≥65 yr old	<65 yr old	≥65 yr old
Amount (V_8)	0.049[b]	0.055[b]	0.053[c]	0.066[c]
Filter duration (V_{14})	0.065[b]	0.010	0.052	0.002
Nonfilter duration (V_{15})	0.064[b]	0.026[c]	0.110[b]	0.037[c]

[a] Adjusted for age and sex.
[b] $P<.005$.
[c] $P<.05$.

DISCUSSION

This study involved incident lung cancer cases from 1980 through 1982 in New Mexico's Hispanic and non-Hispanic whites. We confirmed findings from other populations with regard to dose-response relationships between lung cancer risk and measures of smoking and the reduction of risk that follows smoking cessation. The collection of detailed smoking information approximately 30 years after the widespread introduction of filter cigarettes facilitated an examination of the risks of smoking different types of cigarettes.

We assessed the effects of cigarette type with two distinct modeling approaches and did not find strong benefits from smoking filter cigarettes (tables 7, 8). Cigarette type had differing consequences in the Hispanic and non-Hispanic whites (table 8). On average, the former group had smoked hand-rolled cigarettes for more years (table 6) than the latter group and the smoking habits of the 2 groups may differ in other respects as well (*8*). The findings from the non-Hispanic whites can be more readily generalized to other cigarette smokers in the United States.

In the non-Hispanic whites, we found somewhat higher risks associated with smoking nonfilter cigarettes, but we found no evidence of increasing protection with the extent of filter smoking. While few lifelong filter smokers were included, the OR estimate associated with this pattern was comparable to that for smokers of mixed types. Lubin et al. (*17, 18*) recently reported similar analyses from an extremely large case-control study in Western Europe. The relative risk for lifelong nonfilter cigarette smokers was approximately twice that for

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smokers of filter cigarettes alone. However, dose-response relationships could not be demonstrated between relative risk and the proportion of years nonfilter brands were smoked or with a cigarette tar index. Among sustained smokers, switching from nonfilter to filter cigarettes was associated with a small reduction in risk (*17*). The results from another recent case-control study conducted in Cuba also did not show a convincing association between tar intake and relative risk of lung cancer (*19*). In a prospective study of British male civil servants, tar yield was associated with lung cancer in noninhalers but not in inhalers (*20*). In the United States, investigations spanning the 1960's and 1970's have shown reduced risks in smokers who switched from nonfilter to filter cigarettes (*21–24*). Thus our results are supported by other studies that show the highest relative risks in sustained nonfilter cigarette smokers and no clear evidence of declining risks with increasing use of filter cigarettes. We interpret the apparently discrepant findings in Hispanics as reflecting the higher risks associated with the smoking of nonfilter cigarettes by this group (table 8); as the proportion of filter cigarette smoking decreases, that of nonfilter cigarette smoking rises and risk increases.

In the non-Hispanic whites, the lack of a dose-response relationship with extent of filter smoking may be explained by methodologic and biologic considerations. We could not estimate total tar intake satisfactorily with our questionnaire. Thus the indices of cigarette type that we used may misclassify the subjects' carcinogens. Inaccurate recall of the details of smoking cigarette types may also introduce misclassification. Alterations of smoking pattern following the switch from nonfilter to filter cigarettes may partially compensate for the reduced tar and nicotine yields of the filter products, as assessed by a machine (*5*).

We readily confirmed the reduction in risk that follows cessation of cigarette smoking. The case series included 130 ex-smokers; some had stopped smoking as long as 54 years previously. As in other series (*17*), the risk of lung cancer in ex-smokers, in comparison with that in continuing smokers, declined steadily with the duration of cessation.

Persons reporting that they inhaled cigarette smoke more deeply were at increased risk. The results of other studies on the consequences of reported inhalation practices are conflicting. In the cohort of British doctors, noninhalers had higher lung cancer mortality (*25*). Higenbottam et al. (*20*) reported similar findings from two separate cohort studies: the Whitehall study of British civil servants and the U.S.-U.K.-Norwegian migrants study. In these studies, smokers of 20 or more cigarettes daily, who reported deeper inhalation, had lower lung cancer mortality. Wald et al. (*26*) have suggested that the increased risks in noninhalers reflect increased tar deposition in the proximal airways of the upper lobes. However, other studies, in addition to the present one, have demonstrated higher risks in inhalers than in noninhalers (*18, 19, 27*). Unfortunately, none of the inhalation questions used in these studies have been validated against appropriate physiologic measures. In a study of 10 subjects, Tobin and Sackner (*28*) found that reported inhalation practices were not consistent with actual inhalation pattern, as measured with a nonobtrusive device.

An unexpected finding was the strong interaction between age and duration of cigarette smoking. Both stratified (tables 3, 4) and logistic approaches (table 5) demonstrated a statistically significant reduction in the effect of smoking duration as age increased, but a similar interaction was not present between age and the number of cigarettes smoked. Detection of statistically significant interaction is model dependent (*29*). Since these data were analyzed with logistic regression, the finding of interaction between age and duration implies departure from the multiplicative scale.

In populations with a high incidence of lung cancer, cross-sectional, age-specific incidence and mortality rates generally decline in the older age groups. This decline has generally been considered to reflect cohort-specific smoking patterns, though explanations related to underdiagnosis and selective survival of less susceptible individuals have been offered (*2, 30, 31*). In their analysis of lung cancer incidence in the cohort of British doctors, Doll and Peto (*31*) also detected apparently reduced risk among older smokers. While lung cancer incidence rose uniformly among regular smokers through age 79 years, the incidence rates declined in older men, even when the rates were standardized for the amount smoked.

Although this decline in effect of smoking duration with age may be interpreted biologically, potential sources of bias should also be considered. In discussing this phenomenon in the cohort of British doctors, Doll and Peto (*31*) considered potential underdiagnosis of lung cancer among the elderly. This explanation is not readily applicable to a case-control study, though disease misclassification, differential on smoking status, might increase with age. With increasing age, the intensity of diagnostic evaluation may lessen and clinical diagnoses without histologic confirmation may be more common in the elderly. Accordingly, lung cancer might be diagnosed more often on clinical evidence in smokers but overlooked in nonsmokers. If such bias does occur, the effect would be an increase with age in measures of association between lung cancer and smoking. Alternatively, misclassification of cigarette smoking variables might be more frequent in the older cases because of less accurate recall by older respondents and an increased proportion of surrogate interviews in the older cases. On the basis of preliminary findings from survey data, Harris (*32*) suggested that accuracy of recall of age of starting and stopping smoking declines with increasing respondent age. In the present study, surrogate interviews were needed more often in older subjects, but the findings were unchanged when the analyses were restricted to the subjects who were directly questioned. Finally, the interaction could reflect unmeasured aspects of cigarette smoking that both influenced the respiratory tract dose of carcinogens and were associated with age.

Alternatively, those who develop lung cancer at

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younger ages may be more susceptible to cigarette smoke because of endogenous characteristics or unmeasured environmental factors. The susceptibility explanation implies that the sequence of changes resulting in the development of lung cancer may be influenced by host characteristics and is not solely stochastic.

This study readily confirmed the strong relationship between cigarette smoking and lung cancer. The risk of lung cancer was primarily determined by the amount and duration of cigarette use, but it was modified by types of cigarettes smoked, inhalation practices, and age. However, the findings suggest that the risk of lung cancer in smokers can best be reduced by cessation of smoking.

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Respiratory Cancer in a Scottish Industrial Community: A Retrospective Case-control Study

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Summary

A retrospective case-control study was undertaken as part of an enquiry into possible causes of an epidemic of lung cancer in an industrial town in central Scotland. Relatives of the cases and controls answered a questionnaire which encompassed aspects of the social and occupational personal history of the deceased. Despite the length of time intervening between the period of mortality and this investigation, enough questionnaires were completed to allow the histories of the cases and controls to be usefully compared.

The results indicate that smoking and occupation contributed little to the aetiology of the outbreak of lung cancer in Armadale.

Introduction

In the small town of Armadale in central Scotland, an outbreak of primary lung cancer began in 1968 (Lloyd and Barclay, 1979; Lloyd et al., 1982). The mean standardized mortality ratio (SMR) for primary respiratory cancer from 1969–73 was the highest of all cities, burghs and landward areas in Scotland during that time (Lloyd and MacDonald, 1984). Within the town itself, many of the deaths from lung cancer formed a cluster near a source of air pollution—a steel foundry (Lloyd, 1978a, 1981). This cluster was statistically significant, with an SMR, based on Scottish rates, of 206 between 1968 and 1977. The cases of primary lung cancer had been identified initially by examining the diagnoses on the death certificates of the local parishes in the Registrar General's Office for Scotland. The validity of most of those diagnoses was confirmed later by obtaining supporting information from other sources of diagnostic data (Tyrrell and Lloyd, 1983).

During the earlier stages of the enquiry, the occupational and social backgrounds of the deceased were investigated on a preliminary basis, through the use of hospital case notes, death certificates and discussions with local doctors. No unusual features were identified which would have explained so many cases of lung cancer in such a short period (Lloyd, 1978b; Lloyd et al., 1982). Nevertheless, to test the hypothesis that the cluster of lung cancer might be causally linked to occupation and smoking habits, it was considered essential to undertake more detailed enquiries into the social and occupational backgrounds of the deceased. We decided to construct a questionnaire which would be answered by relatives of the deceased in the form of a retrospective case-control study. Most of the questions concerned details of the smoking habits and occupational experiences of the deceased with additional questions covering personal and familial histories of related lung disease and cancer, and the residential histories.

Methods

The period covered by the study was 1968–74, when the SMR for the town had been found high. The cases were residents of Armadale who had died during 1968–74 with the diagnosis of primary lung cancer on the death certificate. The controls were chosen from a list of residents of Armadale who had died from any cause other than lung cancer, during the same period. Preliminary work had shown that this width of diagnostic frame was necessary to allow matching for the social characteristics in this small population. The cases were computer-matched consecutively for sex, age at death±10 years, year of death±5 years, and by social class I–V. Anticipating the problem of failure to trace some controls, reserve controls were obtained for as many cases as was possible.

Ethical permission was obtained at district and area health board levels for tracing and interviewing next-of-kin or other relatives (hereafter referred to collectively as relatives). The agreement of the local family doctors was also obtained.

Using the experience gained from a pilot study of a similar questionnaire within an occupational workforce elsewhere, a final questionnaire was constructed. Since the major areas of interest were the tobacco habit and occupational history of the deceased, most of the questions covered details of those areas. For smoking history, questions included the average, minimum and maximum numbers of cigarettes smoked daily, the age of starting smoking, the number of years of that habit, the use of pipes and cigars and filter cigarettes, the brand name of the tobacco used (from which the tar content was estimated), the inhalation practice, the habit of smoking at work, and exposure to passive smoking at work and at home. There was also a question on the certainty with which this information was given. For occupational history, questions covered occupations since leaving school, and exposure to specified chemical and physical factors; details were requested of any time spent at particular types of work within the coalmining and steel foundry industries. For the previous medical history of the deceased, questions covered experience of non-malignant respiratory diseases. For the familial medical history, the questions also included cancers and coronary heart disease. The questions on place of residence covered addresses since 1940. These addresses were subsequently assigned to Zones A–E, (*see Fig.* 1), which were aggregates of enumeration districts of the town at the 1971 census and which had been used previously in epidemiological investigations.

Questions also covered residential proximity to industrial sources of environmental air pollution, and the degree to which that pollution inconvenienced the individual concerned. The type of fuel used normally for

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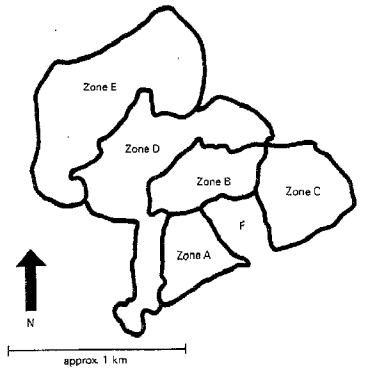

Fig. 1. Zone map of Armadale. Zone A: west of foundry; Zone B: north of foundry; Zone C: east of foundry; Zone D: intermediate; Zone E: distant; F: foundry.

heating and cooking was investigated. Finally, various combinations of factors were examined to try to identify signs of interaction between them in promoting the elevated mortality from lung cancer.

The questionnaire was administered to the nearest surviving relative of the deceased, by one of two interviewers. To avoid interviewer bias, the interviewers were not told whether the person they were interviewing was a relative of a case or of a control. The relatives were traced mainly with the assistance of the local general practitioners and other staff at the only group practice in the town. Where they were unable to identify surviving relatives still living in the area, they were often able to supply names and addresses of friends who knew where the relatives could be found. Other sources used for tracing relatives were a local minister, and, for some of the more unusual names, the local telephone directory.

For those cases and controls whose relatives could not be contacted, other sources of information were used to ascertain only the location of the last known address.

The information derived from the questionnaire was subjected to frequency analysis; and for many exposures, the relative risks and their 95 per cent confidence limits were used to test the null hypothesis that the answers of the cases and controls did not significantly differ from each other.

Results

General

The interviews were carried out between November 1982 and March 1984.

Table I. Age at death of cases and controls

	Age group					
	30–39	40–49	50–59	60–69	70–79	80+
Cases	2 (5%)	1 (2%)	4 (10%)	15 (36%)	14 (33%)	6 (14%)
Controls	0 (0%)	2 (5%)	6 (14%)	15 (36%)	15 (36%)	4 (10%)

Of a possible 137 relatives on the list of interviewees, 103 (75 per cent) were traced and interviewed. Nineteen controls were subsequently eliminated: either they were the 'reserve' controls of cases for which a matched control had already been obtained, or the cases to which they were matched had no known relatives—the relatives having migrated to an unknown location or abroad. The final total of interviews used for the analysis of the data was 84: 42 cases, each with one matched control.

Of the 42 cases of primary lung cancer obtained for the analysis, 35 were males. The age at death of the cases ranged from 37 to 86 years; those of the controls were from 47 to 84 (*Table I*). Because the lapse of time between the year of death and this study taking place was up to 18 years, it was found that many of the spouses of the cases and controls had died. Hence the largest group of informants was the daughter/son group, the second largest being the husband/wife group (*Table II*). Thus, information about 30 of the cases and 32 of the controls was obtained from a close relative (spouse, sibling, son or daughter).

Smoking History

There were no statistically significant differences between the answers of the cases and controls in any of the questions (*Table III*).

More cases than controls were found for those who had ever smoked, for cigarettes only, cigar/pipe smokers and for smokers of plain cigarettes; for small and large numbers of cigarettes smoked, for high tar content of cigarettes; and for inhaling practice.

More controls than cases were found for non-smokers and smokers of filter cigarettes; for medium (15–29) consumption of cigarettes; for being permitted to smoke at work; and for passive smoking both at work and at home.

The cases started smoking at an earlier age (18·7 years) and continued the habit for longer (45·6 years).

There was less certainty about the smoking habits of the controls than about the habits of the cases.

Occupational history

The differences between the number of cases and controls employed in the major industries of the town (coal mines, steel foundry, brickworks), were not statistically significant (*Table IV*). Slightly more cases than controls

Table II. Relationship between respondent and deceased

	Husband/ wife	Son/ daughter	Brother/ sister	Nephew/ niece	Grandchild	In-laws	Other
Cases	13 (31%)	13 (31%)	4 (10%)	7 (17%)	1 (2%)	3 (7%)	1 (2%)
Controls	8 (19%)	17 (41%)	7 (17%)	7 (17%)	1 (2%)	2 (5%)	0 (0%)

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Table III. Characteristics of the smoking history of cases and controls

Category	*Characteristic*	*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
	Never smoked	3	8	1·0	
	Cigarettes only	28	26	2·87	0·68–11·94
	Cigarettes and pipe or cigar	4	4	2·67	0·39–18·16
	Pipe or cigar only	7	4	4·67	0·76–28·47
Ever Smoked: cigarette/pipe/cigar	Smokers	39	34	3·06	0·75–12·44
	Filter cigarettes	6	8	1·0	
	Plain cigarettes	19	12	2·11	0·59–7·61
	Plain and filter	5	4	1·66	0·31–9·01
Mean quantity smoked for duration of habit	1–14 Cigarettes/day	11	7	1·0	
	15–29 Cigarettes/day	10	13	0·49	0·14–1·73
	30+ Cigarettes/day	9	8	0·72	0·19–2·78
Tar content (estimated from brand name)	Low-medium tar	5	7	1·0	
	High tar	21	14	2·1	0·55–7·95
Includes cigar/pipe smokers	Inhaling practice				
	Yes	26	24		
	No	3	6		
	Permitted to smoke at work				
	Yes	10	13		
	No	25	19		
Continual exposure to passive smoking	At work Yes	10	15	0·56	0·21–1·50
	No	25	21	1·0	
	At home Yes	32	34	0·84	0·29–2·45
	No	9	8	1·0	
(in years)	Age started smoking	$\bar{x}$ 18·7 SD 9·1	19·2 8·9		
(in years)	Duration of habit	$\bar{x}$ 45·6 SD12·7	43·7 12·2		
Reliability of information	Very reliable	3	3		
	Fairly reliable	22	14		
	Some idea	6	7		
	Uncertain	3	4		
	Guess	3	2		

* Relative risk = 1·0 identifies baseline category.

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had worked in the coal mines at some time, but fewer had worked in the local steel foundry. Almost equal numbers of cases and controls had worked in the local brickworks. All other occupational groups contained negligible numbers of both cases and controls. Some individuals had worked in more than one industry.

When coal mining and foundry work were categorized according to subgroups of occupation, the biggest difference between cases and controls was for the moulder/coremaker group of foundry workers, with 1 case and 5 controls. For exposure to chemical agents, there were no significant differences between cases and controls.

Personal and familial medical histories

Considerably more cases than controls were reported to have had a history of bronchitis (*Table V*). This difference was statistically significant, with a relative risk of 3·71 and 95 per cent confidence limits of 1·19–11·58.

Due to the difficulties with recall experienced by the relatives, it was not possible to obtain a reliable or comprehensive history of chest disease or of all types of cancer in the families of cases and controls. However, in the data available there were no significant differences between the numbers of relatives of cases and controls for the histories of asthma, lung tuberculosis, and all cancers.

Only slight differences between cases and controls were noted for the types of fuel used for domestic cooking and heating (*Table VI*).

Residential history

Most of the cases and controls had been lifelong residents of Armadale; only 5 cases and 8 controls had ever lived outside the town. Of those who had resided outside Scotland, 4 were cases (2 in the USA, 1 in Australia, 1 in Newfoundland) and 6 were controls (3 in England, 1 in the USA, 1 in France, 1 in Poland).

The modal number of addresses for each person was 2; 16 cases and 17 controls had that number. No person had lived in more than 4 addresses.

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Table IV. Characteristics of the occupational history of cases and controls (numbers include persons who ever worked in the industry)

Category	*Characteristic*		*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
Working history	Other occupations		17	24	1·0	
	Coal mining		21	17	1·74	0·71–4·25
	Steel foundry		9	13	0·98	0·34–2·82
	Brickworks		6	7	1·21	0·35–4·26
Exposure to	Coal dust	Yes	20	15	1·78	0·69–4·60
		No	15	20	1·0	
	Sand, silica, cotton or mineral fibres	Yes	4	4	1·0	
		No	31	31	1·0	
	Metal dust/ fumes	Yes	7	7	1·0	
		No	28	28	1·0	
	Direct and intense heat	Yes	2	2	1·0	
		No	33	33	1·0	
Mine workers only	Surface and/or general		5	4	1·0	
	Faceworker		13	11	0·95	0·20–4·44
	Surface and face-worker		3	2	1·2	0·13–10·99
Foundry workers only	Moulder/coremaker		1	5		
	Furnaceman		1	0		
	Sandblaster		2	0		
	Smith/forger		0	1		
	Specific occupation unknown		4	1		

* Relative risk = 1·0 identifies baseline category.

Table V. Characteristics of the medical history of cases and controls

Category	*Characteristic*		*Cases*	*Controls*	*Relative Risk**	*95% confidence limits*
Personal medical history	Bronchitis	Yes	14	5	3·71	1·19–11·58
		No	27	35	1·0	
	Pneumonia	Yes	6	5	1·21	0·34–1·47
		No	35	35	1·0	
	Pneumoconiosis	Yes	10	7	1·52	0·52–4·49
		No	31	33	1·0	
	Unspecified respiratory	Yes	25	21	1·41	0·58–3·40
		No	16	19	1·0	
Family medical history	Coronary heart disease		11	17	1·0	
	Asthma		1	3	0·51	0·05–5·56
	T.B.		2	0		
	Lung cancer		2	3	1·03	0·15–7·19
	Other cancers		8	3	4·12	0·89–18·88
	Pneumoconiosis		4	8	0·64	0·16–2·61

* Relative risk = 1·0 indentifies baseline category.

Within Armadale, there were no statistically significant differences between numbers of cases and controls who had ever lived in the various zones (*Fig.* 1). More cases than controls had ever lived in Zone A, the area with the cluster of lung cancer deaths (*Table VII*). When the period 1965–74, (i.e. just before and during the time when the SMRs for lung cancer were abnormally high) was examined as a separate unit, the difference between the numbers of cases (12) and controls (8) who had lived in Zone A was even greater (*Table VIII*). The only other zone where the cases exceeded controls was Zone C, directly east of the foundry (*Fig.* 1); during the period 1965–74, 6 cases and 3 controls had lived there.

Table VI. Type of fuel or power used for domestic heating and cooking

	Gas	*Coal*	*Electric*	*Coal and other*
Heating				
Cases	2 (5%)	35 (83%)	1 (2%)	4 (10%)
Controls	1 (2%)	35 (83%)	3 (7%)	3 (7%)
Cooking				
Cases	32 (76%)	6 (14%)	2 (5%)	1 (2%)
Controls	33 (77%)	4 (10%)	3 (7%)	2 (5%)

Fifteen lung cancer cases had no known relatives and were therefore *not* included in the 42 cases in this study.

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Table VII. Ever lived in each zone

	Zones				
	A	B	C	D	E
Cases	14	11	7	17	7
Controls	11	12	4	21	7

Table VIII. Dates of residence in zones A and C

	1940–64	*1965–69*	*1970–74*
Zone A			
Cases	2	11	1
Controls	3	7	1
Zone C			
Cases	0	3	3
Controls	1	1	2

Table IX. Location of last known address of cases and controls whose relatives could not be contacted

	A	*B*	*C*	*D*	*E*
Cases	3	3	1	6	2
Controls	8	6	2	9	5

However, they were matched to 30 controls (some other cases having a reserve control). When their last known addresses were plotted by zone, there were no significant differences in distribution between cases over controls (*Table IX*). Thus there was no bias in the geographical distribution of the cases included in the study.

Of those who were conscious of a neighbouring source of environmental air pollution, the only major difference between numbers of cases and controls was for the combination of steel foundry and brickworks (*Table X*). But the cases did not complain of resulting inconvenience much more than did the controls.

Various combinations of factors, including residence in Zone A were analysed (*Table XI*), but no significant signs of interaction were found which might have contributed strongly to the elevated mortality from lung cancer. The combination of residence in Zone A during 1965–74 and a history of bronchitis showed the greatest difference. A similar difference was found for the combination of heavy smoking (more than 29 cigarettes daily and middle-to-high tar content) and a history of bronchitis. In all comparisons, however, the numbers were too small to allow a reasonable opportunity of finding statistical significance.

Discussion

Despite the long time between the increased incidence of lung cancer and the interviews with the relatives, the

Table X. Proximity to pollution source

Comment	*Variable*	*Cases*	*Controls*	*Relative risk**	*95% confidence limits*
Applies only when residence was within ½ mile of the industry	Steel foundry only	11	11		
	Gas works and foundry	1	1		
	Brickworks, gas and foundry	1	4	0·50	0·01–27·11
	Brickworks, foundry	20	13	3·08	0·86–11·07
	Steelworks, brickworks and coal mine	4	3	2·67	0·42–16·83
Outwith ½ mile proximity		5	10	1·0	
Awareness of atmospheric pollution	Yes	15	12		
	No	27	30		

* Relative risk = 1·0 identifies baseline category.

Table XI. Combinations of factors (3-way tables)

Factors:—
1. Resident in zone A between 1965–74
2. Heavy smoker, i.e. over 29 per day, and middle or high tar
3. Ever worked as miner
4. Ever worked in foundry
5. History of bronchitis

	Cases	*Controls*
① and ②	2	3
① and ③	4	3
① and ④	5	4
① and ⑤	4	0
② and ③	6	6
② and ④	3	2
② and ⑤	6	2
③ and ④ and ①	0	0
③ and ④ and ②	3	0

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number of contacts made and the responses at interview allowed a comprehensive picture to be gained of the occupational and social backgrounds of cases and controls. This experience was similar to that reported in an investigation of asbestos-related mesothelioma (Finlayson et al., 1971).

In general the occupational experiences of both cases and controls were very similar. Some epidemiological studies have suggested that workers in ferrous industries are at a greater risk of dying from lung cancer than persons in the general population; the risk of lung cancer has been related especially to exposure to 'hot metal', with moulders particularly at risk (Morrison, 1957; Hueper, 1966; Radford et al., 1976; OPCS, 1978; Wall, 1980). However, this present study confirmed the results of preliminary work (Lloyd et al., 1982) in finding no evidence to support the association of lung cancer with foundry work in general; nor was an association found with hot metal exposure or with moulding in particular. There were no reports of asbestos or radon exposure. No statistically significant differences were found between the numbers of cases and controls exposed to coal, dust, sand, silica, direct and intense heat from industrial furnace, metal dusts, or fumes from petroleum and its products. Hence, occupational experiences did not appear to have contributed in any important way to the elevated mortality from lung cancer in Armadale. (The similarity between the numbers of cases and controls having a coal mining history and an exposure to coal dust indicated the reliability of the respondents' answers, at least in that context of occupational experience.)

Because the most important cause of lung cancer is known to be cigarette smoking, the questions about smoking habits were very detailed. However, since this study relied on individuals remembering what their relatives were doing up to 15 years previously, we could not obtain as full and comprehensive an account of the smoking habits of the deceased as could be expected in more favourable circumstances. For instance, while it was fairly easy to obtain a figure for the amount of tobacco smoked daily, the respondents found it far more difficult to provide information concerning inhaling practice, and often had difficulty with brand names. However, an examination of the information about the amount, the duration of habit, the types of cigarette smoked, the opportunity to smoke at work, and about passive smoking, showed no significant differences between cases and controls in any factor. For some risk factors, there was an excess of controls. The biggest difference between the groups (19 cases and 12 controls having smoked plain cigarettes) could have been a consequence of the greater amount of missing and uncertain information found with the control group.

When considering familial medical histories it was noted that a history of lung cancer in the close family was as infrequent amongst the cases as amongst the controls. A family history of all other cancers was more frequent with the cases than with controls, but the small numbers in both groups make this finding difficult to interpret.

The high frequency of a history of bronchitis amongst the cases, which was the only statistically significant difference between cases and controls, is consistent with evidence that bronchitis and lung cancer are both associated with air pollution, as well as with cigarette smoking.

Indoor air pollution from cooking and heating appliances has been suspected as a pathogenic factor for respiratory disease (Florey et al., 1979; Lende, 1980). No significant difference in the use of such appliances by cases and controls was apparent in this study. The relatively small difference between numbers of cases and controls who had ever lived in Zone A, an area which was subject to relatively high air pollution (Yule and Lloyd, 1984; Gailey and Lloyd, 1983, 1985) and where an excess of lung cancer had been discovered (Lloyd, 1978a), might have resulted from our inability to eliminate from our controls all those whose deaths could have been linked with the air pollution through causes other than lung cancer. However, because of the small size of the town and hence the small number of deaths each year, deaths from all other causes had to be included as potential controls in order to allow the other characteristics of the cases to be matched. Nevertheless, despite this difficulty in the design of the study, the findings were consistent with the statistically significant excess of cases observed previously in an area close to the site of a polluting industry (Lloyd et al., 1982; Lloyd, 1982).

In summary, this study demonstrated that social and occupational factors were probably not of importance in the outbreak of lung cancer in Armadale during 1968–74. Hence the hypothesis that environmental air pollution might have played a significant aetiological role was not invalidated. The study also illustrated the practicability of undertaking a retrospective study covering a wide range of occupational and social factors by means of questionnaires given to relatives of people who had died up to 15 years before the start of the study.

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LUNG CANCER RISK ASSOCIATED WITH CIGAR AND PIPE SMOKING

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A case-control study of 1,529 histologically confirmed male lung cancer cases and 2,899 controls matched for sex, age, hospital of admission and interviewer was conducted in France between 1976 and 1980. The results presented concern the effects of smoking habits, especially cigar and pipe use, on the occurrence of lung cancer, in a total of 38 exclusive cigar smokers, 61 exclusive pipe smokers and 586 mixed tobacco smokers. Exclusive cigar or pipe use (RR = 5.6 and 1.6 respectively) has been shown less harmful than exclusive cigarette smoking (RR = 13.3), mixed cigar and cigarette smoking (RR = 8.5) and mixed pipe and cigarette smoking (RR = 8.0). Different inhalation practices were observed according to smoking habits: while among exclusive cigarette smokers 29.8% never inhaled the smoke, among exclusive cigar and exclusive pipe users these percentages were 89.5% and 86.9 respectively. No significant increase with greater exposure to cigar was found among mixed cigar and cigarette smokers after adjustment for exposure to cigarettes, defined by duration and daily consumption of cigarettes (RR = 1.20), and by type of cigarettes smoked—light or dark, filter or nonfilter (RR = 1.13). Similar results were observed among mixed pipe and cigarette smokers after adjustment for cigarette exposure (RR = 0.95 and 1.04).

Smoking of pipe or cigar tobacco appears to entail a far lower risk of lung cancer than cigarette smoking (Peto and Doll, 1984). Lung cancer mortality rates for pipe and cigar smokers are about one-quarter of those seen for cigarette smokers in the UK studies, and one-eighth of those in the US studies (Bailey, 1984).

The association between lung cancer and non-cigarette tobacco use has been reviewed in two reports (US Surgeon General, 1979, 1982); several epidemiologic studies have shown higher risks among lifetime cigar or pipe smokers when compared to non-smokers, but lower risks when compared to lifetime cigarette smokers; also, lung cancer risk increased with the amount of cigars or pipes smoked. Some studies have shown that the risk for cigar or pipe smokers, who are also cigarette smokers, appeared to be intermediate between the high risk for exclusive cigarette smokers and the low risk for exclusive cigar or pipe smokers. These results have recently been confirmed (Joly *et al.*, 1983; Lubin *et al.*, 1984*b*).

We now report the results on cigar and pipe use from a case-control study undertaken to evaluate the role of the different types of tobacco on lung cancer.

MATERIAL AND METHODS

An epidemiologic study on lung cancer was conducted simultaneously in 5 European countries with the support of the US National Cancer Institute. In France, a total of 1,625 cases with histologically confirmed lung cancer and 3,091 controls matched for sex, age at diagnosis (± 5 years), hospital of admission and interviewer were included in the study between 1976 and 1980.

The characteristics of this study have been described in previous reports on French data (Benhamou *et al.*, 1985), and on the international data as a whole (Lubin *et al.*, 1984*a*). The results reported here concern all French males interviewed in the study, *i.e.* 1,529 cases and 2,899 controls.

The distribution of histological types of lung cancer according to smoking habits is presented in Table I. Of the 1,529 cases, 1,092 were of squamous type (71.4%), 169 were indifferentiated (11.0%), 133 were adenocarcinomas (8.7%), 4 were of mixed Kreyberg I and Kreyberg II types (0.3%) and 131 were unspecified type (8.6%).

The principal diagnoses among the 2,899 controls were: bone diseases (13.4%), trauma (12.3%), benign tumors (11.2%), viral and other infectious diseases (10.5%), malignant tumors (8.2%), neurological diseases (7.2%) and digestive diseases (3.7%).

The risks associated with exposure to cigarettes, cigars (or cigarillos), pipes or possible associations of these 3 types of tobacco will be detailed. Smokers are defined as people having smoked at least one cigarette, or one cigar or one pipe per day for at least one year. Data recorded about cigarette smokers have been previously described (Benhamou *et al.*, 1985). The following data on cigar and pipe use were collected for each smoker: age at beginning and duration of smoking, frequency and depth of inhalation. In addition, the length of the cigar usually smoked, the two last brands of cigars smoked, and for each the number of cigars per day, was recorded. Similarly, the number of pipes smoked per day was recorded. The daily consumption of cigars has been calculated by dividing the total lifelong number of cigars smoked by the overall duration of smoking in days.

Adjusted RR of lung cancer and 95% CI have been estimated with the Mantel-Haenszel method (Mantel, 1963).

RESULTS

The distribution of the different patterns of tobacco use among males is presented in Table II. Eighty-five percent of the cases and 61% of the controls were lifetime smokers; in contrast, few men were lifetime cigar or pipe smokers: 0.6% and 0.3% respectively among cases, and 1.0% and 1.9% respectively among

Abbreviations: CI, confidence interval; RR, relative risk(s).

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TABLE I - PERCENTAGE DISTRIBUTION OF HISTOLOGICAL TYPES AMONG MALES WITH LUNG CANCER ACCORDING TO SMOKING HABITS

Histological types	Non-smokers	Cigar only	Pipe only	Cigarette only	Cigar and cigarette	Pipe and cigarette	Other types	Total
Total	36	9	5	1298	68	76	37	1529
Squamous	55.6	77.8	100.0	71.8	67.7	80.3	56.8	71.4
Small, oat, spindle	5.6	11.1	—	8.3	14.7	6.6	8.1	8.4
Kreyberg I type not distinguished	5.6	—	—	2.6	2.9	1.3	2.7	2.6
Adenocarcinoma	25.0	—	—	8.5	8.8	2.6	16.2	8.7
Mixed Kreyberg I and II	—	—	—	0.3	—	—	—	0.3
Kreyberg type unspecified	8.3	11.1	—	8.5	5.9	9.2	16.2	8.6

TABLE II - RELATIVE RISKS OF LUNG CANCER ACCORDING TO DIFFERENT SMOKING PATTERNS

Type of tobaccos	Number of cases	Number of controls	RR[1] (95% CI)	p
Non-smokers	36	650	1.0	
Cigars only	9	29	5.6 (2.3–13.5)	<0.001
Pipes only	5	56	1.6 (0.5–4.5)	NS[2]
Cigarettes only	1298	1759	13.3 (9.3–19.1)	<0.001
Cigarettes and cigars	68	144	8.5 (5.4–13.6)	<0.001
Cigarettes and pipes	76	172	8.0 (5.1–12.6)	<0.001
Cigars and pipes	1	19	1.0 (0.1–7.0)	NS[2]
Cigarettes, cigars and pipes	36	70	9.3 (5.3–16.2)	<0.001
Total	1529	2899		

[1]All RR were calculated *versus* non-smokers.–[2]NS: not significant.

controls. When compared to non-smokers, an excess of lung cancer risk ($p<0.001$) was found for: lifetime cigarette smokers (RR = 13.32), mixed cigar and cigarette smokers (RR = 8.53), mixed pipe and cigarette smokers (RR = 7.98) and mixed cigarette, cigar and pipe smokers (RR = 9.29). An increased risk ($p<0.001$) was also found for lifetime cigar smokers (RR = 5.60). In contrast, RR for lifelong pipe smokers (RR = 1.61), although increased, was not statistically significant. This lack of significance may be due to the small number of cases in this smoking category.

Lung cancer risk with years of cigar use was estimated after adjustment for cigarette exposure, defined by duration of cigarette smoking and by number of cigarettes smoked per day. The risk was not significantly increased with greater duration of cigar smoking (RR = 1.20), after adjustment for cigarette exposure (Table III). The same analysis was performed after adjustment for type of cigarette smoked (light or dark) and use of filter. Three categories were defined: the first one concerned those having smoked filter cigarettes for at least half of their tobacco-smoking history, whatever the type of tobacco smoked; the second concerned those having smoked filter cigarettes and also light tobacco for less than half their smoking history; and the last concerned those having never smoked anything but dark tobacco non-filter cigarettes. The lung cancer risk was not significantly increased with greater duration of cigar smoking (RR = 1.13), after adjustment for type of cigarettes smoked (Table IV). The adjusted RR were recalculated with number of cigars smoked per day instead of duration of cigar smoking and similar results were obtained.

The same analyses were performed among mixed pipe and cigarette smokers (Tables V and VI). RR of lung cancer was not significantly increased with greater pipe exposure after adjustment for duration of cigarette smoking and number of cigarettes smoked per day (RR = 0.95) o
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TABLE III - RR[1] OF LUNG CANCER BY YEARS OF CIGAR USE AND BY DURATION AND NUMBER OF CIGARETTES SMOKED (CASES/CONTROLS)

Cigar use (yr)	Duration of cigarette smoking and number of cigarettes/day					Adjusted RR[2] on cigarette smoking characteristics (95% CI)
	0 yr	<35 yr		⩾35 yr		
	0 cig.	<20 cig.	⩾20 cig.	<20 cig.	⩾20 cig.	
<15	1.00 (1/9)	0.56 (1/16)	6.95 (17/22)	2.00 (4/18)	6.35 (12/17)	1.00
⩾15	3.60 (8/20)	1.69 (3/16)	2.81 (5/16)	3.13 (8/23)	9.56 (17/16)	1.20 (0.67–2.17)

[1]All RR were calculated versus only cigar smokers for less than 15 yr.–[2]Chi-square test of homogeneity was not significant.

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TABLE IV - RR[1] OF LUNG CANCER BY YEARS OF CIGAR USE AND BY TYPE OF CIGARETTES SMOKED (CASES/CONTROLS)

Cigar use (yr)	Type of cigarettes smoked				Adjusted RR[2] for cigarette smoking characteristics (95% CI)
	0 cig	Mostly filter	Mostly non-filter, mostly dark	No filter, all dark	
< 15	1.00 (1/9)	1.20 (2/15)	8.18 (10/11)	4.21 (22/47)	1.00
⩾ 15	3.60 (8/20)	1.50 (3/18)	4.20 (7/15)	5.21 (22/38)	1.13 (0.64–1.99)

[1]All RR were calculated *versus* only cigar smokers for less than 15 yr.–[2]Chi-square test of homogeneity was not significant.

TABLE V - RR[1] OF LUNG CANCER BY YEARS OF PIPE USE AND BY DURATION AND NUMBER OF CIGARETTES SMOKED (CASES/CONTROLS)

Pipe use (yr)	Duration of cigarette smoking and number of cigarettes/day					Adjusted RR[2] on cigarette smoking characteristics (95% CI)
	0 yr 0 cig.	< 35 yr		⩾ 35 yr		
		< 20 cig.	⩾ 20 cig.	< 20 cig.	⩾ 20 cig.	
⩽ 10	1.00 (0/5)	1.35 (3/28)	5.10 (9/20)	4.45 (9/23)	13.64 (15/12)	1.00
> 10	1.17 (5/51)	3.86 (6/18)	3.82 (8/24)	3.67 (9/28)	9.87 (17/19)	0.95 (0.56–1.62)

[1]All RR were calculated versus ony pipe smokers for 10 yr or less.–[2]Chi-square test of homogeneity was not significant.

= 0.95) or for type of cigarettes smoked (RR = 1.04). In Tables III and V, age at first cigarette was verified to be similar in each smoking category for mixed smokers. At the same time, in Tables IV and VI, duration and daily consumption of cigarettes were verified to be similar.

A separate analysis was performed among mixed cigar and cigarette smokers who first smoked cigarettes and then changed to cigars. It appears that their lung cancer risk was significantly lower (RR = 0.40, $p<0.01$) than that of lifetime cigarette smokers after adjustment for the whole duration of smoking (*i.e.*, cigarettes plus cigars). The significant decrease in risk was likely to be due to the differences in inhalation characteristics: about 15% of the patients who switched from cigarettes to cigars inhaled cigarette smoke but never inhaled cigar smoke. A similar study was conducted for mixed pipe and cigarette smokers *versus* lifetime cigarette smokers; the adjusted risk was not significantly lower (RR = 0.34), probably because of the small number of patients.

Inhalation

The RR associated with inhalation of cigar, pipe and cigarette smoke according to smoking history, are presented in Table VII. The percentage of cases and controls who never inhaled the cigar smoke was greater among lifetime cigar smokers (67% and 97% respectively) than among mixed cigar and cigarette smokers (50% and 68% respectively). RR of lung cancer were significantly increased ($p<0.05$ linear trend tests) with the frequency of inhalation of cigar smoke for exclusive cigar smokers as well as for mixed cigar and cigarette smokers.

For mixed smokers, the risk remained significantly higher (RR = 2.71 $p<0.06$) when adjusted for inhalation of cigarette smoke. Similarly, among lifetime pipe smokers more cases and controls never inhaled the pipe smoke (100% and 86% respectively) than among mixed pipe and cigarette smokers (59% and 73% respectively). A significant increase in lung cancer risk ($p<0.05$) was found with the frequency of inhalation of pipe smoke among mixed pipe and cigarette smokers; however, this increase in risk disappeared when inhalation of cigarette smoke was taken into account (RR = 1.11). The percentage of cases and controls who never inhaled cigarette smoke was greater in both cigar and cigarette smokers (44% and 57% respectively), and in both pipe and cigarette smokers (29% and 51% respectively) than in lifetime cigarette smokers (24% and 34% respectively). In each smoking category (cigar and cigarette, pipe and cigarette, and exclusive cigarette), an increasing lung cancer risk ($p<0.10$) was found with greater exposure to cigarette smoke. Moreover, half of the mixed cigar and cigarette smokers never inhaled cigar and cigarette smoke, and similarly half of the mixed pipe and cigarette smokers never inhaled pipe and cigarette smoke.

TABLE VI - RR[1] OF LUNG CANCER BY YEARS OF PIPE USE AND BY TYPE OF CIGARETTES SMOKED (CASES/CONTROLS)

Pipe use (yr)	Type of cigarette smoked				Adjusted RR[2] on cigarette smoking characteristics (95% CI)
	0 cig	Mostly filter	Mostly non-filter, mostly dark	No filter, all dark	
⩽ 10	1.00 (0/5)	2.68 (4/18)	4.09 (6/17)	6.01 (26/48)	1.00
> 10	1.17 (5/51)	10.04 (10/11)	7.21 (9/14)	3.67 (21/64)	1.04 (0.63–2.74)

[1]All RR were calculated *versus* only pipe smokers for 10 yr or less.–[2]Chi-square test of homogeneity was not significant.

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TABLE VII – RR[1] OF LUNG CANCER BY FREQUENCY OF INHALATION OF CIGAR, PIPE AND CIGARETTE SMOKE ACCORDING TO SMOKING HABITS

A.

Frequency of inhalation	Cigar smoke inhalation					
	Cigar only smokers			Cigar and cigarette smokers		
	Cases	Controls	RR	Cases	Controls	RR
Never	6	28	3.9	35	101	6.1
Sometimes or rarely	1	0	—	2	15	2.4
Always or usually	2	1	36.1	30	28	19.4
p-value for trend			<0.01			<0.01

B.

Frequency of inhalation	Pipe smoke inhalation					
	Pipe only smokers			Pipe and cigarette smokers		
	Cases	Controls	RR	Cases	Controls	RR
Never	5	48	1.9	45	125	6.5
Sometimes or rarely	0	6	—	15	23	11.8
Always or usually	0	2	—	16	24	12.0
p-value for trend						<0.05

C.

Frequency of inhalation	Cigarette smoke inhalation								
	Cigar and cigarette smokers			Pipe and cigarette smokers			Cigarette only smokers		
	Cases	Controls	RR	Cases	Controls	RR	Cases	Controls	RR
Never	30	82	6.6	22	88	4.5	312	598	9.4
Sometimes or rarely	3	15	3.6	10	23	7.9	116	185	11.3
Always or usually	35	47	13.4	44	61	13.0	870	973	16.1
p-value for trend			<0.07			<0.01			<0.06

[1]All RR were calculated *versus* non-smokers.

DISCUSSION

Several studies have shown that pipe and cigar smokers have higher lung cancer mortality rates than non-smokers, but a lower risk of developing lung cancer than cigarette smokers (US Surgeon General, 1979). The results in our study are consistent with those reported in the literature: in relation to rates for non-smokers, lung cancer risks for lifetime cigar and lifetime pipe smokers (RR = 5.60 and 1.61 respectively) were increased, but to levels below those seen for lifetime cigarette smokers (RR = 13.32). Moreover, mixed cigar and cigarette smokers, and mixed pipe and cigarette smokers, were at intermediate levels of risk (RR = 8.53 and 7.98 respectively). These results are similar to those reported in the overall international case-control investigation (Lubin *et al.*, 1984*b*). The lack of significance of most relative risks associated with pipe smoking is likely to be due to the small numbers of pipe smokers.

The low number of patients in our study having smoked cigars or pipes exclusively can be explained by the fact that, in France, the sale of cigars and pipe tobacco represents a very slight proportion of that compared to cigarettes. For example, in 1980, cigarette sales were 13 times higher than cigar sales (Hill and Flamant, (in press).

The differences in levels of risk can be explained by inhalation patterns: the vast majority of exclusive cigarette smokers inhale smoke, whereas most exclusive cigar or pipe smokers do not (Lubin *et al.*, 1984*b*). Similarly, the proportion of both cigar and cigarette smokers who inhale is intermediate between that of exclusive cigar and exclusive cigarette smokers (Lubin *et al.*, 1984*b*). These differences in inhalation practices could be explained by a greater alkalinity of the smoke of pipes or cigars which is more irritating to the respiratory tract; and therefore reduces the depth of inhalation (Bailey, 1984).

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"PROGRESS ON JOINT ENVIRONMENTAL AND OCCUPATIONAL CANCER STUDIES (SESSION VIII EPIDEMIOLOGY (CANCER IN LOUSIANA (CASE-CONTROL STUDIES OF ENVIRONMENTAL DETERMINANTS IN HIGH RISK PARISHES)))"

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"LUNG CANCER (CURRENT STATUS AND PROSPECTUS FOR THE FUTURE (EPIDEMIOLOGY AND CLASSIFICATION (3 ENVIRONMENTAL ASSOCIATIONS WITH LUNG CANCER IN TEXAS COASTAL COUNTIES)))"

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Lung cancer and women: Results of a French case-control study

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Summary Ninety-six women with histologically confirmed lung cancer and 192 matched controls were involved in an international case-control study conducted from 1976 to 1980. The aim of this study was an examination of the effects of different smoking habits, especially the type of cigarettes smoked (light or dark tobacco and filter or nonfilter use) on the occurrence of lung cancer in French females. All these patients were either nonsmokers or lifetime cigarette smokers. Matched relative risk (RR) of smokers compared to nonsmokers was found to be increased for both Kreyberg I (RR = 6.6) and Kreyberg II (RR = 2.1) categories; however, this increase was significant ($P < 0.0001$) only for Kreyberg I lung cancer. A significant increase ($P < 0.0001$) in matched RR was found with early age at first cigarette smoked, daily consumption, duration of smoking, frequency of inhalation, use of dark tobacco and use of nonfilter cigarettes. Matched RR associated with smokers not always using dark tobacco and those smoking only dark tobacco as compared to nonsmokers were significantly increased (trend test $P < 0.0001$). On the contrary, the increase of RR was not significant when either daily consumption, or duration of smoking, or age at first cigarette was taken into account. Lung cancer appeared to be associated with daily consumption and use of nonfilter cigarettes in a matched logistic regression.

The incidence of lung cancer among women is increasing in most industrialized countries. In recent years, the rate of increase among women has been greater than among men. However, the mortality rate of lung cancer among males is still very much higher than in females: for instance, in the United States, it has been reported to be twice as high as in females (Starzik, 1983). Most authors concur in the belief that, if this trend persists in the United States, lung cancer will be the major cause of death by cancer among women, instead of breast cancer – as observed now in California, Washington and Louisiana (Loeb *et al.*, 1984) – and lung cancer death rates for females may equal those for males by the year 2000 (Starzik, 1983). This evolution is associated with an increase in cigarette consumption among females over the past 20 to 30 years (Fraumeni & Blot, 1982). The situation in France is, however, unusual insofar as lung cancer mortality in females is low compared to other industrialized countries (Hirohata *et al.*, 1982) and increased only very slightly between 1952 and 1982 (INSERM, 1980; 1984).

A large number of epidemiologic studies on lung cancer have been reviewed in two reports of the Public Health Service (Office on smoking and health, 1980; 1982). Over the past thirty years, the association between lung cancer and tobacco consumption (principally cigarettes) among males has been demonstrated, and in some recent investigations among females, lung cancer and the use of tobacco have also been found to be associated, though less strongly (Office on smoking and health, 1980).

This paper reports the results observed among females of a case-control study undertaken to evaluate the role of cigarette smoking habits, especially the type of cigarettes smoked (dark or light tobacco and filter or nonfilter use) in the causation of lung cancer.

Materials and methods

An epidemiologic study on lung cancer was conducted simultaneously in France and in four other European countries Austria, Germany, Italy (Milan, Rome), and Scotland with the support of the US National Cancer Institute. In France, this case-control study was performed from 1976 to 1980. A total of 1,625 cases with histologically confirmed lung cancer and 3091 controls whose current diseases were not tobacco-related were included. Each case was matched with two controls for sex, age at diagnosis, hospital of admission and interviewer. A complete description of this study can be found in previous papers (Lubin *et al.*, 1984; Benhamou *et al.*, 1985). The results presented here are those observed in females: that is, 96 cases and 192 matched controls.

Of these 96 cases, 50 cancers were squamous (52%), 16, undifferentiated (17%), 24, adenocarcinoma (25%) and 6, unspecified (6%). The first two histological categories (squamous and undifferentiated) constitute the Kreyberg I category (66 cases), and the third (adenocarcinoma type) constitutes the Kreyberg II category (24 cases).

Among the 192 controls, the main diagnostic categories were: bone diseases (21%), malignant tumours (14%) excluding respiratory tract, oesophagus, liver, pancreas, bladder and kidney, trauma (13%), viral and other infective diseases (8%), benign tumours (4%) and neurological diseases (3%).

Analytical method

Adjusted RRs of lung cancer were estimated using the Mantel–Haenszel method (Mantel, 1963), and 95% CI with the use of the Cornfield (1956) method. The different parameters characterising the smoking habits have been analysed by a logistic regression (Breslow & Day, 1980) taking into account the full matching of each case with her two original controls. In order not to eliminate matched strata, nonsmokers were retained in the analysis. The coding used allows the definition of all possible combinations of cigarette exposure, and the definition of the referent category (nonsmokers) by combining nonsmokers with the lowest level of exposure for three of the four variables used.

Results

Mean age at diagnosis and educational level do not differ significantly either between cases and controls, or between Kreyberg I and Kreyberg II cases (Table I).

Smoking habits

All smoking cases and controls used only cigarettes. The

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Table I Distribution of Kreyberg I and Kreyberg II lung cancer cases and their controls by age at diagnosis and educational level

	Kreyberg I (66) n %	*Controls* (132) n %	*Kreyberg II* (24) n %	*Controls* (48) n %
Age at diagnosis (years)				
<40	1	2	0	2
40–49	11	13	21	17
50–59	39	38	29	33
60–69	29	25	29	29
≥70	20	22	21	19
Mean age (±2 s.e.)	59.3 (2.4)	59.7 (1.8)	59.9 (4.2)	59.4 (3.1)
Education (years)				
<8	61	62	62	69
8–13	36	30	38	27
≥14	3	8	0	4
Mean years (±2 s.e.)	7.0 (0.9)	6.9 (0.6)	5.8 (1.4)	6.2 (0.9)

percentage of regular smokers, i.e. people having smoked at least one cigarette per day for at least one year was, of course, significantly greater ($P<0.0001$) among cases (48%) than among controls (17%). It was, moreover, significantly higher ($P<0.05$) in Kreyberg I cases (55%) than in Kreyberg II cases (29%). The matched RR of smokers relative to nonsmokers in the Kreyberg I category was 6.6 ($P<0.0001$). On the contrary, in the Kreyberg II category, the excess of risk for smokers *versus* nonsmokers (RR = 2.1) was not significant, probably due to the low number of cases (Table II).

Separate study of the different parameters measuring the exposure to cigarettes, among the 96 cases and 192 matched controls, showed an increased matched risk in smokers compared to nonsmokers for the following parameters: age at first cigarette, daily consumption, frequency of inhalation and duration of smoking (Table III). Trend tests were highly significant for each of these four variables ($P<0.0001$).

In this study, 58% smokers smoked dark tobacco exclusively. Three categories of smokers were defined: the first comprised those having smoked dark tobacco for half

Table II Matched RR of lung cancer of smokers to nonsmokers

	Kreyberg I				*Kreyberg II*			
	Cases	*Controls*	*RR*[a]	*95% CI*	*Cases*	*Controls*	*RR*[a]	*95% CI*
Nonsmokers	30	109	1.0		17	41	1.0	
Smokers	36	23	6.6[b]	3.0–14.4	7	7	2.1	0.7–6.4

[a]All matched RR were calculated *versus* nonsmokers. [b]$P<0.0001$.

Table III Matched RR of lung cancer according to variables characterizing cigarette consumption

	Cases	*Controls*	*RR*[a] *(95% CI)*	*Trend test P-value*
Nonsmokers	50	159	1.00	
Age at first cigarette smoked (yrs)				<0.0001
>30	4	6	1.77 (0.48–6.55)	
21–30	15	13	3.72 (1.61–8.58)	
≤20	27	14	8.16 (3.99–19.64)	
No. of cigarettes smoked per day				<0.0001
<10	5	14	1.23 (0.41–3.73)	
10–19	11	11	2.88 (1.16–7.15)	
≥20	30	8	19.97 (5.96–66.93)	
Duration of smoking (yrs)				<0.0001
1–20	3	13	1.17 (0.34–3.62)	
21–40	28	15	6.21 (2.79–13.82)	
≥41	13	5	9.45 (2.62–34.17)	
Inhalation				<0.0001
No	15	18	2.80 (1.25–6.28)	
Yes	31	15	6.58 (3.11–13.94)	
Type of tobacco				<0.0001
≤50% dark	12	13	2.87 (1.20–6.89)	
51–99% dark	4	4	4.77 (1.06–21.42)	
100% dark	30	16	6.10 (2.91–12.77)	
Use of filter				<0.0001
≤50% non filter	17	20	2.54 (1.21–5.31)	
51–99% non filter	12	9	7.15 (2.25–22.77)	
100% non filter	17	4	16.01 (4.72–54.33)	

[a]All matched RR were calculated *versus* nonsmokers.

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of their tobacco history or less (≦50% dark); the second, those having smoked dark tobacco for more than half of their tobacco history (>50% dark) and the last, those having never smoked anything but dark tobacco (100% dark). Similarly, considering the use of filters, three categories were defined: the first comprised those having smoked nonfilter cigarettes for half of their tobacco history or less (≦50% nonfilter); the second, those having smoked nonfilter cigarettes for more than half of their tobacco history (>50% nonfilter), and the last, those having always smoked nonfilter cigarettes (100% nonfilter). A significant increase ($P<0.0001$) of lung cancer matched risk was found with the type of tobacco smoked and with the use of nonfilter cigarettes (Table III). An increased risk, although not significant, was found for 100% dark tobacco *versus* ≦50% dark tobacco users (RR = 2.04) after adjustment for age. On the contrary, the excess of risk for 100% nonfilter *versus* ≦50% nonfilter users (RR = 4.44) was significant ($P<0.03$).

All the parameters described above were studied together in a matched logistic model. This method allowed the estimation of *RR* for each variable when adjusting on the others. Table IV shows a significant excess of risk associated with daily consumption ($P<0.03$) and use of nonfilter cigarettes ($P<0.06$). An increase of risk, although not significant, was found with duration of smoking and frequency of inhalation. The significance of age at first cigarette and type of tobacco disappeared as soon as duration was introduced into the model, so that these two covariates were not taken into account in the final model. However, the small number of cases and controls, associated with the strong correlations of the smoking-related-variables do not allow a clear interpretation of these results. The effect of the type of tobacco was studied using a matched logistic regression (Table V). Two categories of tobacco smokers were defined (100% dark tobacco users or not). RR associated with each category of smokers as compared to nonsmokers were significantly increased (trend test $P<0.0001$). On the contrary, the increase of RRs were not significant when either daily consumption or duration of smoking, or age at first cigarette was taken into account.

Among smokers, 19.5% cases and 27.3% controls were ex-smokers. The excess of risk of current smokers to ex-smokers was not statistically significant and though the

Table IV Results of the multivariate analysis of characteristic parameter of smoking habits in cases and matched controls

Variables	*Log likelihood*	*RR (95% CI)*	*P value (trend)*
No variable	−105.47		
All variables	−81.84		
No. of cigarettes/day	−83.72[a]		<0.03
Nonsmokers		1.00	
<10		0.57 (0.11–2.59)	
10–19		0.89 (0.18–4.44)	
≧20		4.85 (0.66–35.64)	
Use of filter	−83.15[a]		<0.06
≦50% nonfilter[b]		1.00	
>50% nonfilter		1.27 (0.27–5.95)	
100 nonfilter		3.62 (0.68–19.18)	
Duration of smoking, yr	−82.03[a]		NS
≦20[b]		1.00	
21–40		2.10 (0.49–8.96)	
>40		3.27 (0.44–24.14)	
Inhalation	−81.87[a]		NS
Never[b]		1.00	
Mostly or always		1.54 (0.44–5.45)	

[a]Value represents the log likelihood function when the corresponding covariate is removed from the all variables model. [b]The less exposed category includes nonsmokers.

Footnote Considering nonsmokers as referent category for each of the 4 variables, the regression model is overparametrised. The coding used allows the definition of all possible and logical combinations of cigarette exposure, and the definition of the referent category (nonsmokers) by combining nonsmokers with the lowest level of exposure for 3 of the 4 variables introduced in the model. For each covariate, the risk presented in the Table, adjusted on the other covariates, is estimates *versus* the defined referent category. However, in the risk function, as soon as cigarette consumption defined *versus* nonsmokers is introduced, the estimated risk is calculated *versus* nonsmokers.

Table V Matched RR (95% CI) of lung cancer by type of cigarettes smoked

	RR	*RR adjusted on daily consumption*	*RR adjusted on duration*	*RR adjusted on age at first cigarette*
Nonsmokers	1.00	1.00	1.00	1.00
Not always dark	3.20 (1.43–7.16)	1.06 (0.36–3.07)	1.32 (0.44–3.88)	1.56 (0.51–4.80)
Always dark	5.94 (2.86–12.31)	0.74 (0.19–2.86)	1.86 (0.58–5.95)	2.21 (0.62–7.88)
Trend test	<0.0001	NS	NS	NS

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number of years since cessation is greater among controls (11.4) than among cases (5.1), the difference was not significant.

Discussion

General critical comments on the protocol of this international case-control study have been presented in recent papers on the total international data (Lubin *et al.*, 1984) and about French data in men (Benhamou *et al.*, 1985).

Smoking-related variables found to be significantly associated with Kreyberg I, were also found to increase the risk of adenocarcinoma (Lubin & Blot, 1984). In this study, the association between cigarette smoking habits and lung cancer among females was found to be significant ($P < 0.0001$) for the Kreyberg I category. The small number of women with adenocarcinoma can explain the lack of significant difference in the association between lung cancer and cigarette exposure.

The analysis of the different measures of exposure to cigarettes need to be interpreted cautiously because of the relatively small number of women. However, because of the low incidence of female lung cancer in French women, the same amount of time was necessary to include these 96 cases as was needed for the 1,529 male lung cancer cases of this study. This low number of cases is likely to explain why risks associated with classical variables such as duration of cigarettes, although increased, were not significant in the multivariate analysis; moreover, proper effects of type of tobacco and use of filter could not be evaluated simultaneously. In spite of these reservations, the results observed for filter use are consistent in matched univariate analysis and matched logistic regression, i.e. a more harmful effect of nonfilter compared to filter use. The effect of dark compared to light tobacco, though increased, is not significant, probably because of the small number of patients smoking light tobacco.

The usual differences reported in the distribution of the different histologic types of cancer among females, compared with those observed among males (Office on smoking and health, 1980, 1982; Lubin & Blot, 1984) are also found in our study: the percentage of Kreyberg I cases was greater among males (82%) than among females (69%); and, contrary to this, Kreyberg II lung cancer was more frequent among females (25%) than among males (9%). Also, as described in other studies (Office on smoking and health, 1980, 1982), within each histologic type, the percentages of smokers are quite different: in our study, among males and females, the percentages of nonsmokers among adenocarcinoma (8% and 71% resp.) are greater than among Kreyberg I cases (2% and 45% resp.).

The results of this study confirm those of the literature, i.e. a stronger association between lung cancer and cigarette smoking among males than among females, and among Kreyberg I than among adenocarcinoma. However, the lower risk of lung cancer observed for women than for men, must be interpreted cautiously. Indeed, in our sample, although the mean age at diagnosis was similar among male and female cases, tobacco habits were very different for male and female populations with Kreyberg I lung cancer. Among smokers, the average age at first cigarette among women (23 yrs) was significantly greater ($P < 0.001$) than among men (19 yrs). The average number of cigarettes smoked per day among women was 22, and the average duration of the smoking habit was 34 years. These figures were lower than those observed for men (24 cigarettes per day, and 38 yrs resp.). Similarly, for women with lung cancer, the percentage of subjects who inhaled deeply was 36%, the percentage of lifetime dark tobacco smokers was 69% and the percentage of exclusive nonfilter cigarettes smokers was 33%. For men, these percentages were higher (37%, 91%, 65% resp.).

Thus, the lower risk of Kreyberg I lung cancer for women *versus* men could be partially explained by these differences in smoking habits. However, the substantial percentage of nonsmokers among women with lung cancer, especially adenocarcinoma, is consistent with the implication of risk factors such as hormones exclusive to women (Lubin & Blot, 1984).

Concerning lung cancer in women, the situation in France is very special, since lung cancer mortality in females is low compared to other industrialized countries (Hirohata *et al.*, 1982) and has increased only very slightly between 1952 and 1982. This can be explained by later smoking patterns in French women compared, for instance, to American women and we can expect a higher frequency of lung cancer in French women over the next few years.

Existence of a 25 to 30 year interval before the marked increase in consumption of cigarettes by women as compared to men (Hill & Flamant, 1985), suggests that current figures may not yet constitute, particularly in France, a demonstration of the maximal health effects of smoking in women.

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Toward the Decline of Lung Cancer

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Recent declines in the rate of lung cancer among young adults in the United States and Europe cannot be explained completely by reductions in the prevalence of current smoking. The effect of other factors on trends in lung cancer incidence and mortality are discussed, including the role of smoking cessation, alterations in the tar and nicotine content of cigarettes, occupational exposure, air pollution, and nutrition.

Key words: lung cancer decline, smoking cessation, low-tar yield cigarettes, occupational exposures, air pollution, nutrition

During the past four decades there has been a dramatic increase in the incidence of lung cancer in men throughout much of the world. Lung cancer is the leading cause of cancer death in men in most countries, and in 1985 it will be the leading cause of cancer mortality in women in the United States [1]. An examination of sex-specific incidence rates in this country demonstrates a steady increase in the number of new cases of disease, especially among the older cohorts. The rate of increase is declining among younger men, while among women the incidence rates are still climbing rather sharply.

Data from the National Center for Health Statistics show a drop in age-specific mortality among men born after 1930 and possibly among women born after 1940 [2] (see Figs. 1, 2). Among white males, decreases in the incidence rates for cohorts aged 25–34 years were found in both the Third National Cancer Survey [3] and in the more recent Surveillance, Epidemiology End Results (SEER) data [4]. Increases in lung cancer incidence for white men aged 35–44 did not peak until about 1970, when the Third National Cancer Institute data were collected, declining somewhat by the end of the 1970s. Mortality rates among this group decreased from 15 to 12 per 100,000 per year between 1969 and 1979 [5]. While mortality rates among white males between 35 and 44 years of age were stable during the 1970s, increases were still being recorded among the older age cohorts. Incidence and mortality data indicate that rates may also be declining among women under 35 years of age, although sample sizes are too small to be certain [5].

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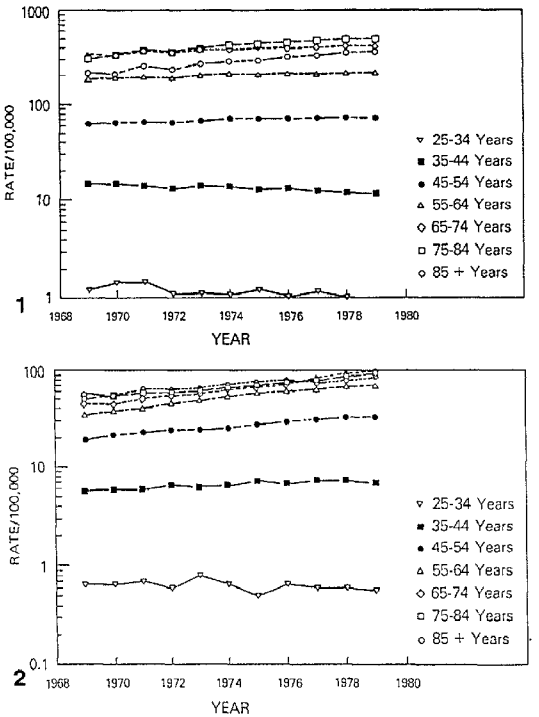

Fig. 1. Age-specific US lung cancer mortality trends among white males. Reprinted from Devesa et al, with permission [5].

Fig. 2. Age-specific US lung cancer mortality trends among white females. Reprinted from Devesa et al, with permission [5].

The purpose of this communication is to review possible reasons for secular trends in the incidence and mortality for lung cancer. The extent to which changing patterns of tobacco consumption in the United States and the rest of the world have contributed to these trends will be considered in addition to the role of smoking cessation, alterations in the tar and nicotine content of cigarettes, occupational factors, air pollution, and diet. It is hoped that this epidemiological exercise will add to the understanding of factors that may affect the downward trend of lung cancer incidence in younger, United States' male cohorts.

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RESULTS

Tobacco Consumption

Smoking habits, especially in the United States, have undergone significant change during the past few decades. In 1955, over one half (54%) of the adult (≥20 years) male population and 27% of adult females were present smokers of cigarettes [6]. Adult cigarette smoking decreased among men by 1965 to 49% and increased among women to 32%. By 1980, it was estimated that these percentages had declined to 38% of adult men and 30% of adult women. Among men, this decline was greatest among the youngest and oldest age groups, with a 33% decline among 20–24 year-olds and a 37% decline among men over the age of 65 (Table I).

The decrease in the proportion of cigarette smokers between 1965 and 1980 was not as great among women. There were 22% fewer smokers among women aged 20–24 and an increase of 75% among women over the age of 65, from 10% in 1965 to 17% in 1980.

Consistent with these changes in smoking patterns, the proportion of never-smokers by age cohort has also changed [2] (Fig. 3). The percentage of never-smokers in the population increased for all men less than 45 years of age and for women less than 35 years old. Almost one-half of the men below the age of 25 had never smoked cigarettes in 1980 compared to less than one-third in this age group in 1965. Among women below 25 years of age, 50.8% claimed to be never-smokers in 1965 versus 56.3% in 1980. Thus, by 1980, young adult men and women were smoking to about the same extent.

What effect will this change in smoking habits have on lung cancer rates? It has been established that trends in mortality rates from lung cancer closely parallel changes in per capita cigarette consumption after a sufficient lag period has elapsed. Thus, the increased smoking prevalence in men born between 1910 and 1930 and in women born between 1920 and 1950 in the United States no doubt led to the "epidemic" of lung cancer occurring in the 1970s and 1980s [2]. This displays the strong coherence of the association of smoking behavior by birth cohort and subsequent mortality experience. In England and Wales, where per capita cigarette smoking plateaued earlier than it did in the United States, there has been a steady decline in the number of deaths from lung cancer, especially among younger male cohorts,

TABLE I. Percentage Change in the Proportion of Present and Former Smokers Among Adults in the United States by Sex, 1965 vs 1980

Age group (years)	Percent change in proportion			
	Present smoker[a]		Former smokers[b]	
	Male	Female	Male	Female
20–24	−33	−22	+34	+51
25–34	−29	−28	+40	+45
35–44	−27	−40	+34	+97
45–64	−21	−4	+53	+99
≥65	−37	+75	+69	+215
All ages ≥65	−27	−13	+50	−91

[a]Present smoker has smoked at least 100 cigarettes and non smokers include occasional smokers.
[b]Former smokers stopped smoking at least 1 year prior to interview.
From the Surgeon General, 1982 [2].

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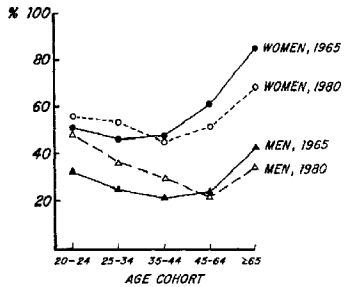

Fig. 3. Percentage distribution of those who have never smoked cigarettes in the United States by age and sex, 1965 vs 1980. From the Surgeon General, 1982 [2].

presumably as the relative proportion of smokers in the younger generations diminishes.

To illustrate this point, a comparison of mortality data from different time periods is informative [7] (Table II). In investigating the trend of decreasing mortality from lung cancer among the younger cohorts of men, the 50% decline in death rates cannot be adequately explained by the 20% decline in smoking prevalence [8]. Similarly, an analysis of prospective data of 10,000 males has shown that only 55% of the difference in lung cancer incidence between geographic areas in Finland and Norway between 1953 and 1962 could be predicted by variations in smoking habits [9]. A second analysis of these data, using risk indices for 1975–1979, displayed a slightly better fit (64%) when plotted against the original smoking indices for 1962, but still left over one third of the variation unexplained [10].

Smoking Cessation

There is no doubt that the cessation of tobacco smoking stops the increase in excess risk associated with continued use of tobacco products [11–15]. In a case-control study conducted by our group [16], we found that among subjects who had smoked for 20 years or more, cessation of cigarette smoking did not alter the risk of lung cancer for about 3 years, followed by a gradual decline in risk approaching that for a nonsmoker after 10 to 15 years. The speed of the decline was dependent on the history of the amount and duration of smoking. The lag period for the reduction in risk associated with smoking cessation is affected in part by selection bias. For instance, smokers with symptomatic conditions will often quit smoking because of discomfort or their physician's advice. This effect diminishes with time, because of selective mortality, since people in poor health will die more rapidly than people in good health.

US trends in smoking cessation correspond inversely to secular patterns in the proportion of current smokers. Between 1965 and 1980, the proportion of ex-smokers among adults in the United States increased from 20 to 30% among men and 8 to 16% among women (see Table I). Increases in the relative proportion of ex-smokers in the population were greater with increasing age for both sexes. Also, the increased

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TABLE II. Decreases in Lung Cancer, Comparing 1978 Data With Data for the Worst-Affected Generations of Men in England and Wales and in the United States

	England and Wales				United States			
	Worst-affected generation (born ca 1910–1911)[a]		Rates for 1978 compared with those for worst-affected generation		Worst-affected generation (born ca 1910–1911)[a]		Rates for 1978 compared with those for worst-affected generation	
Age (years)	Mortality/ million men	Period of observation	Mortality/ million men in 1978	Decrease (%/year)[b]	Mortality/ million men	Period of observation	Mortality/ million men in 1978	Decrease (%/year)[b]
30–34	40	1941–45	17	58/35	24	1958–62	17	30/18
35–39	98	1946–50	63	36/30	73	1963–67	62	15/13
40–44	253	1951–55	138	45/25	219	1968–72	192	12/8
45–49	597	1956–60	385	36/20	502	1973–77	480	4/3
50–54	1,234[c]	1961–65	1,047	15/15	?	1980	1,021	—[e]
55–59	2,219[d]	1966–70	1,912	14/10	?	1985	1,647	—[f]
60–64	3,577[d]	1971–75	3,315	7/5	?	1990	2,625	—[g]
65–69	5,018	1978	5,018	—	?	1995	3,557	—[g]

[a]These are the generations with the highest death rates at ages 35–44, when substantial effects of smoking first became evident. However, if in the future the number of cigarettes smoked per individual will decrease, or the effective dose of noxious chemicals per cigarette will decrease, the benefits at some particular attained age to these two worst-affected generations may be greater than to the immediately previous generations. The maximum American lung cancer rates in old age may therefore be seen, at around the turn of the century, in the generation born in the few years before this "worst-affected" generation.

[b]Percentage decrease, comparing age-specific mortality in 1978 with that for the worst-affected generation (born 1910–11 in England and Wales, born 1927–28 in the United States).

[c]Might have been materially larger but for changes in cigarette composition.

[d]Would have been materially larger but for changes in cigarette composition.

[e]US mortality at ages 50–54 years should reach a maximum by ca 1980.

[f]US mortality at ages 55–59 years is still rising.

[g]US mortality at ages 60–64 and 65–69 years is still rising rapidly.

Reprinted from Doll and Peto [7], with permission.

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percentage of former smokers during the 15-year period was larger among women than among men within each age category. This may be accounted for, in part, by the much larger percentages of ever-smokers and former smokers among men. For instance, 28% of men over the age of 64 were categorized as former smokers in 1965 compared to 4% of women. These percentages increased to 47% of men in 1980 (representing a 69% increase) and 14% of women (representing a 215% increase).

To what extent has smoking cessation contributed to the apparent reversal in the spiralling rate of lung cancer deaths? It was noted earlier that cigarette smoking cessation would not immediately produce a reduction in risk of lung cancer for smokers, but would certainly prevent large increases in risk similar to those experienced by continuing smokers. While it is difficult to assess fully the effects of tobacco smoking cessation on recent trends in lung cancer mortality, several prospective studies present evidence that smokers who quit do indeed reduce their risk of lung cancer. Data from 20 years of observation on male British doctors showed that mortality decreased with the duration of cigarette smoke cessation, although at the end of 15 years it was still two times that of never-smokers [12]. Two other prospective studies, the Multiple Risk Factor Intervention Trial (MRFIT) [17] in the United States and the Whitehall Study of London Civil Servants in England [18] have examined the relationship of smoking cessation to lung cancer risk. The MRFIT Study, including 12,866 high risk (heavy cigarette consumption, high blood pressure, high serum cholesterol) men, showed 81 deaths from lung cancer in the intervention group compared to 69 deaths among the usual care group after 7 years of follow-up. The difference between these mortality rates was not significant. Smoking intervention, including basic behavioral modification techniques and hypnosis, reduced the proportion of ever cigarette smokers in the study group from 63.8 to 32.3% after 72 months. The proportion of ever-smokers among the usual care group was reduced from 63.5% to 45.6% after 72 months. This study might be used to support the contention that smoking cessation does nothing to reduce the risk of lung cancer. One needs to ask, however, whether a reduction in mortality should have been expected. Participants in the MRFIT program were selected specifically because they were considered at high risk of coronary heart disease. They were generally all heavy smokers at the outset of the trial. American Cancer Society data on smoking cessation show that long-term smokers (20 or more years) of a pack or more of cigarettes per day had much less substantive risk reduction than did people smoking less than a pack per day before quitting [19,20] (Table III). When mortality ratios for ex-cigarette smokers compared to never-smokers were analyzed by years of smoking cessation, quitters for 10 years or more had mortality ratios of 1.08 among light smokers in contrast to 1.50 among heavy smokers. Thus, substantial reductions in mortality were not as apparent in previously heavy smokers. The MRFIT participants were not only

TABLE III. Mortality Ratio of Current Cigarette Smokers and Ex-smokers*

No. of cigarettes smoked per day	Current cigarette smokers	Stopped (years)		
		1	1–10	10+
<20	1.61	2.04	1.30	1.08
20+	2.02	2.69	1.82	1.50

*The mortality ratio of men who never smoked was set at 1.00.
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heavy, long-term smokers, but the follow-up data reported were only for a 7-year period—perhaps too short to demonstrate a significant change.

A report of 10 years of observation in the Whitehall study, a randomized trial of smoking cessation in 1,445 male smokers aged 40–59 years who were at high risk of cardiorespiratory disease, showed a small, significant difference in mortality between the intervention group (I) and normal care group (NC) [18]. The I group, consisting of 714 smoking men, were given advice on smoking cessation, while the NC group of 731 men were left alone. Lung cancer death rates were reduced to a similar extent in participants of both groups who gave up smoking. Overall, lung cancer mortality was 23% lower in the I group (calculated as the estimated proportionate reduction in 10 year risk), although this reduction was not significant. Two reasons for the absence of an effect may have been that 1) the one third of smokers who gave up cigarettes in the I group continued to smoke pipes and cigars, and 2) while a decline in lung cancer risk among heavy smokers may be expected by the end of 9 years, differences in the number of cigarettes smoked per day in the I and NC groups were small, averaging three or four cigarettes by the final postal inquiry.

Tar and Nicotine Yields

The dose-response relationship found between the risk of lung cancer and the number of cigarettes smoked per day prompted the belief that lower tar in cigarettes would lead to a diminution in the risk of lung cancer. Reports in the literature have been ambiguous regarding the effects on mortality of these reductions in tar yield [21–33], although there now appears to be a clearer picture of possible benefits [23]. Peto and Doll [34] have proposed that much of the decreasing rate of lung cancer in British men before the age of 50 years may have resulted from the introduction of the filter-tipped cigarette. The British data show that the younger cohorts smoke 20% fewer cigarettes than the older cohorts—a difference that does not alone account for reductions in the rate of lung cancer found among men under the age of 45 years (see Table II). This finding conforms with expectations, since individuals who are less than 50 years will have been smoking cigarettes on average since the middle 1950s when substantial tar reductions in cigarettes were taking place. Changes in mortality rates that have occurred in cohorts older than 50 years are difficult to assess, since the majority of these patients began smoking with nonfilter cigarettes. Thus, studies of trends in mortality for this age group will include a large number of people who smoked low-tar cigarettes for only a fraction of their smoking lives (Goodman and Wynder, unpublished data, 1985) (Figs. 4, 5). Other problems such as smoking compensation, changes in cigarettes smoked per day, and tobacco smoke inhalation may also affect these findings. For instance, between 1965 and 1980, the percentage of male adult ($\geq$20 years) smokers who smoked at least 25 cigarettes per day rose from 25 to 34%, while the proportion of individuals smoking less than 15 cigarettes per day fell from 28 to 23% [6] (Fig. 6). Among women, these percentages were even more divergent, rising from 14 to 24% of individuals smoking more than 24 cigarettes per day and falling from 44 to 34% of women smoking less than 15 cigarettes per day.

The tar yield of both filter-tipped and nonfilter cigarettes in the United States and in most other industrialized societies has declined sharply over the past few decades (Fig. 7). Smokers who do not compensate in full for the reduction in nicotine by smoking more cigarettes, puffing more frequently or with greater volume, or by

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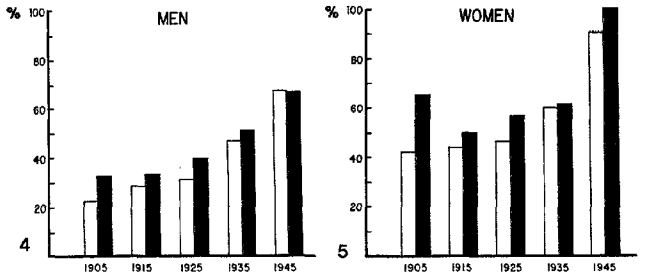

Fig. 4. Filter cigarette usage as a percentage of lifetime smoking experience by birth cohort. Open bars, cases (N = 969). Closed bars, controls (N = 1,938).

Fig. 5. Filter cigarette usage as a percentage of lifetime smoking experience by birth cohort. Open bars, cases (N = 375). Closed bars, controls (N = 749).

inhaling more deeply can expect to decrease their risk of lung cancer somewhat. Such a decrease would occur primarily among long-term smokers of low-yield cigarettes (ie, < 10 mg tar). An assessment of the effect of these changes in smoking habits is difficult because, to date, relatively few smokers have smoked low-yield cigarettes for more than 10 years: about 2% of our male and 4% of our female controls. As suggested in a recent report [33] and in accordance with our data, it is probable that the risk of lung cancer may be measured in direct proportion to the tar yield of the preferred brand of cigarettes smoked, once appropriate adjustment has been made for duration and amount.

Occupational Factors and Air Pollution

Although there is a large attributable risk of smoking to lung cancer, there is no doubt that lung cancer is a multifactorial disease. A number of occupational exposures have been established as risk factors for lung cancer, including exposure to arsenic, asbestos, bischloromethyl ether, chromium, ionizing radiation, mustard gas, nickel, and polycyclic hydrocarbons in soot, tar, and oil [35]. Furthermore, these substances may not be representative of the full spectrum of potential carcinogens. Weak risk factors to which a large proportion of the population is exposed may produce substantial changes in the background of lung cancer deaths. Since many of the substances listed above have been in use for less than the average induction period for lung cancer, it is probable that current mortality reflects early stages in what may be an upward trend in rates. Doll and Peto [7] have criticized the Occupational Safety and Health Administration estimates [36] of the proportion of all cancers attributable to occupation (20% or more) on the basis of what they deem to be severe overestimation of the number of individuals in the United States who are heavily exposed to occupational carcinogens.

It is difficult to separate the effects of smoking and socioeconomic status from occupational and other factors [37] (Fig. 8). For instance, there is a strong interaction

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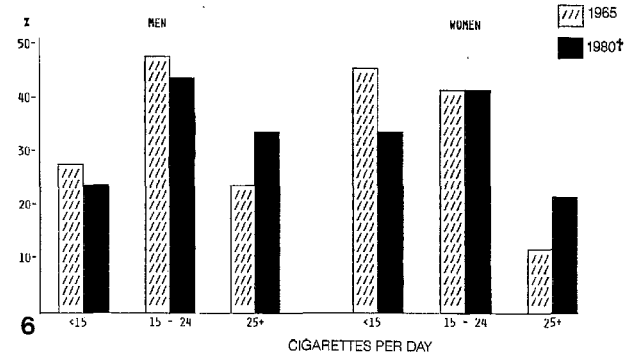

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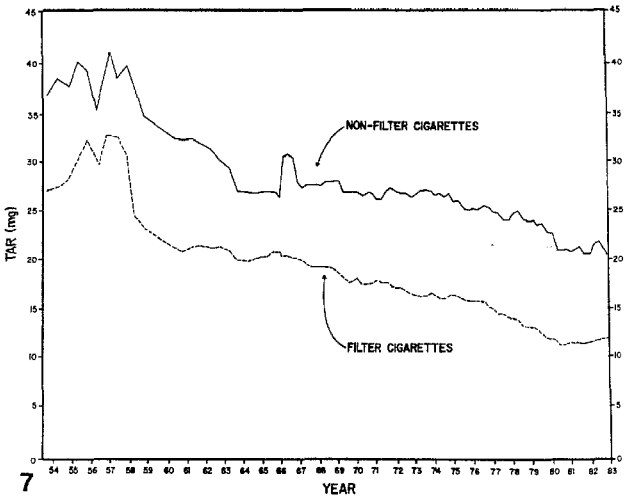

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Fig. 6. Percentage distribution of adult current smokers by grouped number of cigarettes smoked per day and sex, 1965 vs 1980. A current smoker has smoked at least 100 cigarettes and now smokes (includes occasional smokers). The 1980 data are for the last 6 months of 1980. From the Surgeon General, 1983 [6].

Fig. 7. Sales-weighted average tar deliveries, 1954–1983.

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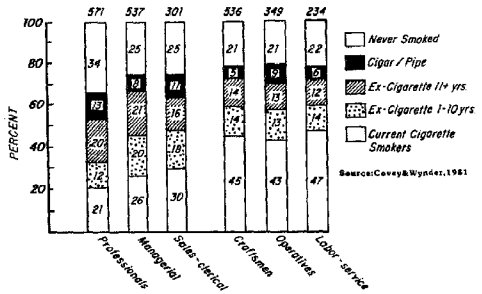

Fig. 8. Age-standardized smoking rates by occupational level of white male controls aged 41 through 70 years. Reprinted from Covey and Wynder [37], with permission.

between smoking and asbestos on the risk of lung cancer. The importance of testing for synergy between smoking (and socioeconomic status?) and these occupational exposures seems particularly important in view of the fact that there appears to have been no increase in the proportion of never-smokers developing lung cancer over the past 35 years [2,6]. Doll and Peto [7] attributed approximately 11,000 lung cancers to occupational factors in the United States, comprising 15% of male and 5% of female lung cancers. They recommend, and we concur, that there is a strong need for a case-control study based on a representative sample of US cases to clarify the relationship between smoking and occupation and the rate of lung cancer.

Air pollution has been investigated quite extensively in association with the risk of lung cancer because of the direct route of exposure and urban/rural differences in the rate of lung cancer unexplained by variations in tobacco consumption [38]. A large number of pollutants have been identified as carcinogens based on animal and occupational evidence [39,40], which has led to speculation of a causal relationship. The low rate of lung cancer in nonsmoking Seventh-Day Adventists living in Los Angeles or Greeks and Japanese living in heavily polluted Athens and Yokohama suggests that if there is an effect of air pollution on lung cancer risk it is small at best.

Nutrition

Another consideration is whether improvements in the dietary status of young adults may have added to the current trends in the decline of lung cancer incidence in the United States among this group. The role of dietary fat, fruits and vegetables, vitamin A, retinoids, and other micronutrients in the etiology of lung cancer has been the subject of a great number of recent investigations. Examinations of nutritional factors in the induction of lung cancer are difficult not only because of the overwhelming affect of tobacco smoke on risk but also as a result of the problems inherent in obtaining reliable dietary information. These problems have been reviewed by us in some detail in an earlier article [41]. As a result of these and other research obstacles, it is premature to come to any conclusions regarding the effect of nutritional excesses, deficiencies, or imbalances on the incidence of lung cancer. In spite of these reserva-

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tions, two prospective studies with sample sizes large enough for appropriate statistical analysis provide suggestive evidence that daily consumption of green-yellow vegetables reduces the risk of lung cancer [42,43]. The relatively low incidence of lung cancer in Japan compared to that in the United States while caused, in large part, by differences in smoking patterns, may also be influenced by dietary differences [43]. Although the comparatively low consumption of fruits and green and yellow vegetables in Japan in the past would be inconsistent with the hypothesized protective effect of β-carotene, the intake of dietary fats, which may also enhance lung carcinogenesis, is also lower.

Doll and Peto [7] have posited that a reduction of US lung cancer deaths by 20% may be brought about by dietary means. We regard this issue as open. Investigations of macro- and micronutrients, especially of carotinoids on lung cancer risk are indicated. Case-control studies of lung cancer and nutrition must be conducted in a manner allowing for appropriate adjustment for smoking habits and socioeconomic status. Furthermore, we need to recognize that it may not be possible to obtain reliable dietary histories from cancer patients. Prospective studies with large-scale blood collection and storage for later analysis should be initiated to resolve the issue [44].

DISCUSSION

When the link between tobacco smoking and the risk of lung cancer was established in the early 1950s, it was apparent that the incidence of lung cancer would soon become the leading cause of cancer death among men and, perhaps in the future, among women. This prediction has unfortunately been realized.

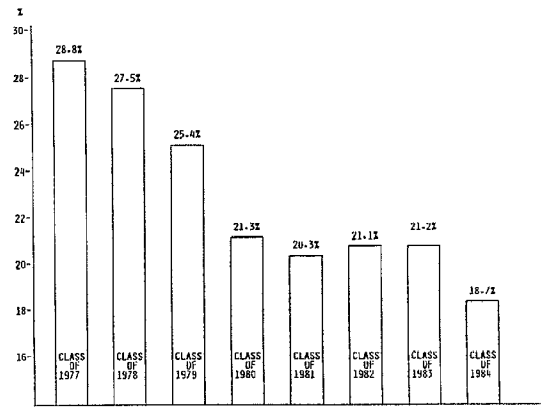

Fig. 9. Teenage smoking trends: daily smoking by high school graduates. Reprinted from the National Institute on Drug Abuse [47], with permission.

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Following the release of the first Surgeon General's Report in 1964 [45] there have been gradual changes in smoking habits in the United States in addition to overall reductions in the tar yields of cigarettes. First, there was a sharp increase in males who quit smoking, especially among the middle-aged, upper-income groups. This was followed by a rise in the proportion of never-smokers among young men. These trends have led to an approximate 50% reduction in the percentage of male smokers compared to rates 30 years ago.

Women have also begun to stop smoking in increasing numbers, although not to the same extent as men. The overall percentage of female smokers, however, has doubled since 1950. Hence, the rate of new lung cancer cases continues to climb, and it is expected that the rate of this incline will not fall off for years to come.

Superimposed on these changes in the prevalence of cigarette smoking is the fact that the tar yield of American-manufactured cigarettes is about one half of what it was in 1950. Since most smokers are unlikely to compensate completely for this decline in tar yield, it is likely that smokers of low-tar yield cigarettes will reduce their risk of lung cancer significantly, an effect mostly to be seen among young cohorts. Efforts to reduce further the tar yields of cigarettes on the market should continue. The average tar yield of cigarettes should not exceed 10 mg.

Obviously, occupational carcinogens need to be controlled to the greatest extent possible. Air pollution, though unlikely to affect the risk of lung cancer, should be monitored and reduced for other public health reasons such as general hygiene. At this time, no specific dietary advice can be given for the possible prevention of lung cancer.

Those of us who have been involved in etiological research on tobacco-related cancers may derive some satisfaction from the turnaround in the lung cancer rates in most of the developed world. Anti-smoking campaigns have been obviously successful and should now focus on high risk groups such as women and lower income smokers. Young people should be admonished not to start smoking or, if they have already done so, to quit. That these preventive efforts have been fruitful is evidenced by a recent report released by the National Institute on Drug Abuse showing that the prevalence of teenage smoking continues to decline [46] (Fig. 9). The reduction in the risk of lung cancer in individuals who quit offers a special incentive to those in public health whose goal is the elimination of a preventive disease. We who have expended a great deal of energy toward the reduction of lung cancer and the tobacco-related diseases can now see light at the end of the tunnel.

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ALDERSON, MR.

"RISK OF LUNG CANCER, CHRONIC BRONCHITIS, ISCHAEMIC HEART DISEASE, AND STROKE IN RELATION TO TYPE OF CIGARETTE SSMOKED, PASSIVE SMOKING AND OTHER FACTORS (ARTIFICIAL SPLIT, ½)"

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ALDERSON, MR.

"RISK OF LUNG CANCER, CHRONIC BRONCHITIS, ISCHAEMIC HEART DISEASE, AND STROKE IN RELATION TO TYPE OF CIGARETTE SSMOKED, PASSIVE SMOKING AND OTHER FACTORS (ARTIFICIAL SPLIT, 2/2)"

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CHERKASSKII, V.B.

"HISTOLOGICAL PATTERMS OF LUNG CANCER AND ENVIRONMENTAL FACTORS (TRANSLATED FROM RUSSIAN)"

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VUTUC, C.

"PROCEEDINGS OF THE FIFTH WORLD CONFERENCE ON SMOKING AND HEALTH, WINNIPEG, CANADA, 1983 (II HEALTH CONSEQUENCES (LUNG CANCER RISK AND TAR YIELDS OF CIGARETTES SMOKED))"

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National Lung Cancer Conference

(September 23–25, 1987)

Held at Clatterbridge Hospital, Merseyside, UK.

Abstracts of Invited Papers

The epidemiology of lung cancer in the West of Scotland – Pointers for the future?

C.R. Gillis & D.J. Hole

West of Scotland Cancer Surveillance Unit, Ruchill Hospital, Glasgow, UK.

The West of Scotland has some of the highest rates of both lung cancer and heart disease recorded. If an epidemiological study of cigarette smoking and lung cancer showed differences from those previously reported it might point to new approaches. A case-control study of 656 males with twice that number of non-smoking related controls has shown a linear increase in the relative risk of heart disease, but little increase in relative risk of lung cancer above an average exposure of 15–24 cigarettes per day (the cell type determined in 90% of cases studied). Despite the reduction in tar content since levels were first measured, medium tar cigarettes still conferred high relative risk if more than 15 cigarettes per day were smoked. None of these findings are explained by smoking practices peculiar to the West of Scotland. Smokers returned to the risk of lung cancer in non-smokers following 20 years of ex-smoking.

A cohort of 15,399 apparently healthy males and females aged 45–64 was examined between 1972 and 1976 by multiphasic screening for cardiovascular risk including measurement of blood pressure, ECG, serum cholesterol and FEV1. These were entered into the cancer registry in 1972. By December, 1986, 2711 of these have died and the cohort mortality for lung cancer shows, for equal amounts smoked, that the West of Scotland population is at more than twice the absolute risk of lung cancer than any of the cohort studies in the literature.

Also an increasing dose response relationship for lung cancer was found comparing controls, passive smokers (relative risk = 2.4). those who smoked and smokers who lived in households where at least one other member of the household smoked.

The rates of lung cancer in those now living in green field sites in the new towns around Glasgow but who lived within the City of Glasgow in the 1950s were only slightly lower than in Glasgow itself. So the additional risk of lung cancer from either passive smoking or atmospheric pollution does not account for the West of Scotland excess which continues to be observed compared to other Scottish cities.

Serum cholesterol readings from those apparently healthy individuals measured at least 4 years prior to the diagnosis of lung cancer or any other cancer show that high serum cholesterol levels were associated with low rates of lung cancer, contrary to many published findings.

This and the surprising nature of the dose-response relationship allow speculation about the existence of a genetic component in the aetiology.

An epidemiological study has been carried out of knowledge and opinion in Glasgow, Manchester and Leeds about symptoms and signs that may mean cancer. While knowledge improved with increased inputs of education, education itself appeared less important than other variables (age, sex, family experience of cancer, social class) in determining knowledge.

Education on lung cancer prevention in schools

A. Charlton

Cancer Research Campaign Education and Child Studies Research Group, University of Manchester, UK.

Probably the least effective way to prevent lung cancer is to teach about lung cancer prevention. When the link between lung cancer and smoking became clear, it was generally assumed that if people were familiarised with this association they would not smoke.

In a study by the author in 1979, children who smoked were significantly more likely than nonsmokers, to state that smoking can cause lung cancer. Bewley and her colleagues showed that although children could name diseases associated with smoking they did not understand the meaning. Diseases which might strike at the age of 40 or over are much too distant to have any meaning for children. Some children enjoy the added excitement of risk. Others are made very anxious if their parents smoke and lectures about health risks can be very boring.

It is nevertheless imperative that something should be done to prevent children from smoking, as Doll and Peto have shown that the risk of lung cancer increases the earlier smoking is started.

Regular two-yearly surveys carried out by the OPCS now show the prevalence of smoking among children. Nearly 30% of young people are regular smokers at school-leaving age. The prevalence is higher among the less academically inclined. A large CRC-funded study showed that among 16 to 18-year-olds at vocational colleges the prevalence of regular smoking was 31% whilst in the same age group in the sixth forms it was 12%. The same survey showed that children whose parents smoke are nearly twice as likely to be smokers; whilst parents' approval is associated with a seven times increased rate. Only 2% of children would smoke if they thought their best friend was not in agreement.

Young smokers are likely to attend more discos more often than the nonsmokers; to attend gigs more often; to drink alcohol more often. Young smokers are already more likely than nonsmokers to express positive views about smoking e.g. that it calms the nerves, keeps the weight down, gives confidence. Perhaps this is related to advertisement-awareness because smokers were significantly more likely than nonsmokers to have a favourite cigarette advertisement.

Conference Chairman: J.A. Green, CRC Department of Radiation Oncology, Clatterbridge Hospital, Bebington, Merseyside, L63 4JY, UK (to whom requests for reprints should be sent).
Conference Secretary: S.W. Watkin.

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Projections of Lung Cancer Mortality in the United States: 1985–2025[1]

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Charles C. Brown,[2] *Larry G. Kessler*[3,4]

Lung cancer has been the leading cause of cancer death in the United States for the larger part of this century. Increases in smoking prevalence from the 1900s through the 1950s have resulted in more than 100,000 deaths annually. Because of the changes during the last three decades in smoking prevalence, the decreasing tar content of cigarettes, and the increasing popularity of low-tar cigarettes, trends in lung cancer are difficult to predict. This article presents an analysis of smoking and lung cancer data using an age-period-cohort model for projecting lung cancer mortality through the year 2025. The projections are based on the initial parameterization of the model and on prevention objectives related to smoking behavior established by the National Cancer Institute. It is concluded that the recent trends in lung cancer are unlikely to be affected by changes in cigarette composition and consumption in the near term, but increasing the effectiveness of anti-smoking campaigns can have a considerable effect on lung cancer rates in the more distant future. [J Natl Cancer Inst 1988; 80:43–51]

Trends in lung cancer mortality during this century have been among the most remarkable phenomena in health statistics. From a relatively rare killer of both men and women in the early 1900s, lung cancer has developed into one of the biggest public health tragedies of the century, now claiming over 100,000 lives each year (*1*). Cancers of the lung and bronchus have been the most frequent cause of cancer death

ABBREVIATIONS USED: HIS = Health Interview Survey; ICD = International Classification of Diseases; NCI = National Cancer Institute.

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[4] We thank Dr. Ronald Wilson, National Center for Health Statistics, for providing unpublished data from the U.S. Health Interview Study. We also thank Dr. David Byar, Dr. David Levin, Dr. Ed Sondik, Dr. Ben Hankey, Dr. Mitchell Gail, Dr. Steven Piantadosi, and Dr. Julian Peto for their comments and suggestions. In addition, we express our gratitude to Ms. Helen Triolo for tireless computer assistance and to Ms. Caroline Ball for typing and editorial assistance.

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of males in the United States for the past 40 years and were the second most frequent cause of cancer death among U.S. females for the past two decades. Recently, lung cancer has nearly surpassed breast cancer in age-adjusted mortality rates for women (*2*).

Because lung cancer is such a major contributor to the overall U.S. cancer mortality picture, its reduction is of the greatest priority among all the various groups involved in cancer control. However, the implementation of effective cancer control strategies and their evaluation will depend to some degree on what is likely to happen to lung cancer trends in the absence of any new major cancer control activities. The purpose of this article is to present projections of lung cancer mortality rates through the remainder of this century and the first three decades of the next. These projections are of considerable interest to the public health community not only because they will suggest the coming mortality for one of the major causes of death, but also because they reflect the general health burden for a variety of diseases related to smoking.

Although studies showing that cigarette smoking is the major determinant of lung cancer were presented to the scientific community as early as 1950, it was not until the first Surgeon General's report on smoking and cancer in 1964 that this relationship was established in a widely accepted public forum (*3*). Therefore, it is not surprising in reviewing the evidence concerning cigarette smoking patterns in the United States that the decades between the end of the First World War and the Surgeon General's report were marked by a substantial increase in the per capita consumption of cigarettes, with a particularly rapid growth during the Second World War (*4*). Because there is a considerable lag time between beginning smoking and the development of cancer [e.g., Doll and Peto (*5*)], the effects of the tremendous increase in smoking have been seen in the lung cancer mortality statistics in the decade of the 1970s.

Two phenomena of recent decades may have led to the beginning of changes in the lung cancer picture for the 1980s and beyond (*4*). Recent data have shown considerable declines in the smoking prevalence among U.S. males, but slower declines for U.S. females (*6,7*). These declines among men began with the release of the 1964 Surgeon General's report and continued with the removal of cigarette advertising from television. Reduction in tar content of all brands of cigarettes and the introduction of low-tar brands beginning in the late 1960s should also lead to lower lung cancer risks even without prevalence changes.

Changes in the prevalence of smoking and tar content of cigarettes have already affected U.S. incidence and mortality rates for men under age 55 (*8,9*). However, no such decline is yet seen in women, which no doubt reflects their dramatic increases in smoking prevalence during the 1960s and 1970s.

These complex changes in smoking behavior over time have lead to morbidity and mortality patterns that have engendered much research (*10-16*). These articles have generally attempted to explain the distinct patterns in lung cancer mortality by various models, sometimes taking explicit account of smoking trends. Despite the use of a variety of models fitting available mortality data, there has been little published to date on projections of those trends. One such projection by Janerich (*17*) using a simple model suggests that lung cancer mortality will continue to rise at a rapid rate and will dominate mortality trends for the near future. Fortunately, this rapid increase is not likely to be realized, as recent reports (*8*) continue to show the decline in lung cancer incidence among U.S. males. Clearly, a sophisticated modeling approach to these trends is needed and, preferably, one that takes into account available data on past smoking behavior.

Subjects and Methods

The analyses presented in this article are based on the numbers of deaths from malignant neoplasms of the trachea, bronchus, and lung (ICD 162-163.0, eighth revision) occurring among white males and females in the United States during 1958-1982. We have not used data prior to 1958 because the ICD coding changed at this time. The data, numbers of deaths and person-years at risk, have been aggregated into 12 age groups (30-34, 35-39, . . ., 80-84, ≥85) and 5 calendar year periods (1958-1962, . . ., 1978-1982). Person-years at risk are approximated by mid-year population estimates.

Our estimates of past smoking prevalence are derived from cigarette smoking histories from the 1978-1980 HIS conducted by the U.S. National Center for Health Statistics. Details of the HIS, a stratified, household-based, personal interview survey, are reported elsewhere (*18*). The respondents in this survey numbered 22,990 males and 26,725 females age 17 or older at the time of the interview. Less than 1% of the interviews were proxies and were not included in our analysis. For each individual, a history of smoking status was derived from answers to the questions of current smoking status, age started smoking regularly, and the time since last smoked regularly. Those who never smoked cigarettes regularly were classified as nonsmokers for their life. Former smokers were classified as nonsmoking from the age they reported cessation of regular smoking. Those reported as ever smoking with partially missing information were classified according to the following assumptions: 1) When the age at initiation of regular smoking was unknown (<0.5%), the modal age of 18 was used; 2) when a self-reported former smoker's time since cessation was unknown (1.6%), the time was assumed to be zero; 3) individuals who were coded as having unknown current smoking status but did report an age of initiation (0.2%) were treated as current smokers.

Because cigarette smokers have higher mortality rates than nonsmokers, estimates of past cigarette smoking prevalence based on currently living persons will understate the actual prevalence. We therefore followed the approach of Harris (*6*) to correct for this bias. Using his notation, we let P_{tu} and Q_{tu} denote the proportions of current and former smokers at age t among respondents alive at age $u > t$. An

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estimate of the prevalence of cigarette smoking at age t, $u - t$ years in the past, is given by

$$P_{tt}(u) = \frac{P_{tu}/S_{tu}}{P_{tu}/S_{tu} + Q_{tu}/F_{tu} + (1 - P_{tu} - Q_{tu})/N_{tu}}, \quad [1]$$

where S_{tu}, F_{tu}, and N_{tu} represent the probabilities of surviving from age t to age u for current smokers, former smokers, and never smokers, respectively. Estimates of S_{tu} and N_{tu} are from the American Cancer Society study (Garfinkel L: personal communication). We did not have estimates of F_{tu}, so, assuming former smokers would experience mortality more similar to that of smokers than never-smokers, we used S_{tu} to represent their survival.

The 3 survey years provided three estimates of the age-specific smoking prevalence for each year in the past. These were combined into a single estimate weighted by the number of persons interviewed. For example, individuals aged 70 and interviewed in 1978, those aged 71 and interviewed in 1979, and those aged 72 and interviewed in 1980 contributed to the estimate of the proportion of smokers aged 42 in 1950.

Because the trends over time in lung cancer morbidity and mortality are strongly related to changes in cigarette smoking and the composition of cigarettes (*4,19,20*) and because the latent period for lung cancer occurrence may be 20–40 years, past changes in smoking behavior and cigarette composition should be an important aspect of any projection of future lung cancer rates. The prevalence of cigarette smoking has been changing from one birth cohort to the next (*6*), and the introduction of low-tar cigarettes has greatly reduced the average tar content of cigarettes sold in the United States (fig. 1). Whereas changes in smoking prevalence should produce birth cohort effects in the trends of lung cancer mortality, changes in cigarette composition affecting smokers across different birth cohorts at the same calendar time should produce calendar period effects in the lung cancer mortality trend.

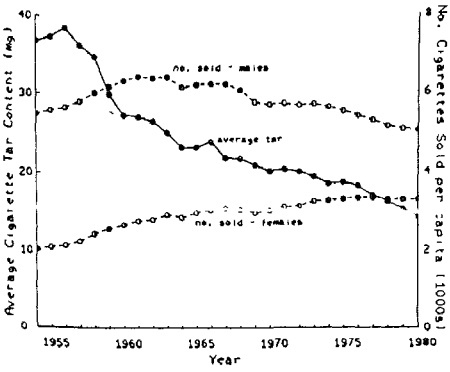

Figure 1. Average tar content of cigarettes sold and age-adjusted smoking prevalence of adults in the United States, 1954–1980.

For these reasons we have based our statistical analysis of lung cancer mortality on an age-period-cohort model (*21,22*). This type of statistical model has been used previously for cohort analyses of lung cancer (*23,24*) but has not been used to project future disease occurrence. This model assumes that the number of cancer deaths D_{ij} observed in age group i during calendar period j follows a Poisson probability distribution with mean $\mu_{ij} = N_{ij}r_{ij}$, where N_{ij} denotes the size of the population at risk and r_{ij} denotes the rate of cancer mortality. The r_{ij} are modeled as a function of age, calendar period, and birth cohort. More specifically, it is assumed that

$$\log(r_{ij}) = A_i + P_j + C_{I-i+j}, \text{ for } i = 1,2,\ldots,I \text{ and } j = 1,2,\ldots,J, \quad [2]$$

where A_i ($i = 1,2,\ldots,12$) denotes the age effect for ages 30–34, 35–39, . . ., 80–84, ≥85; P_j ($j = 1,2,\ldots,5$) denotes the period effect for calendar periods 1958–1962, 1963–1967, . . ., 1978–1982; and C_k ($k = 1,2,\ldots,16$) denotes the cohort effects for birth cohorts 1869–1877, 1874–1882, . . ., 1944–1952.

The model is then fit to the data by maximum likelihood methods. A linear dependency ($k = I - i + j$) exists among the three factors age, calendar period, and birth cohort, which induces a nonidentifiability of the linear components of the three sets of parameter estimates (*25–27*). This nonidentifiability means that we cannot estimate the linear component of trends over time for the period and cohort effect parameters. Therefore, we cannot determine whether the period effect parameters are increasing while the cohort effect parameters are decreasing or vice versa. The nonlinear components of each factor, however, are estimable (*26*). Unfortunately, the increasing or decreasing linear trends of the individual period and cohort factors are often of primary interest.

A number of solutions have been proposed for this nonidentifiability problem. Most of these involve constraints to be placed on the parameters; however, the parameter estimates have been shown to be sensitive to the choice of constraint (*27*). The change in parameter estimates from use of one constraint to another can be so extreme as to preclude meaningful interpretation. Therefore, unless there is a very compelling reason for choosing a particular constraint, this approach will not provide a satisfactory solution. Another method, proposed by Day and Charnay (*23*), requires two or more populations, one of which can be adequately fit by a two-factor model. We found this approach was not applicable because we could not satisfactorily describe either the male or female deaths by a two-factor model. Other proposed solutions involve finding the single three-factor model that is "closest" to the best fitting two-factor model (*25,28*). However, these approaches are ad-hoc statistical solutions that have no biological justification.

Rodgers (*29*) suggested that a valid solution could be obtained by replacing one of the factors with a more directly relevant variable for which the factor is thought to be an indirect indicator. This is the approach we have used here. As suggested by Day and Charnay (*23*) in their analysis of lung cancer in Slovenia and Finland, one would expect the trend of changing cigarette tar content to be reflected in lung

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cancer mortality as a calendar period effect acting across all age groups. Therefore, we followed Rodgers' approach by replacing the period parameters in equation 2 with a regression variable related to the average tar content and number of cigarettes sold. Thus our model is

$$\log(r_{ij}) = A_i + BX_j + C_{I-i+j}, \quad [3]$$

where the period parameter of equation 1 is replaced by a regression on X_j which denotes a measure of the population's exposure to cigarette tar during the jth calendar period.

Results

To fit the model in equation 3 to the observed lung cancer mortality data, we evaluated two exposure measures for the variable X_j: (1) the average tar content of cigarettes sold in the United States and (2) the product of average tar and the number of cigarettes sold per capita (age ≥20) as a measure of the entire population's average exposure level. Figure 1 shows the changing average tar content of cigarettes sold (*30,31*) along with estimates of the number of cigarettes sold per capita to males and females for the period 1954–1980. Our estimates of the sex-specific numbers of cigarettes sold are derived from age-adjusted smoking prevalence estimates applied to the total annual cigarette sales. Our smoking prevalence estimates are based on applying the estimator in equation 1 to the HIS data to derive age-specific prevalence rates aggregated into 5-year age groups. Table 1 shows that the age-specific prevalences of past smoking as estimated from the 1978–1980 HIS generally agree (an average difference of 3.6%) with prevalences estimated from actual surveys conducted in 1966, 1970, and 1975. We then used the 1970 standard U.S. population age distribution to obtain direct age-adjusted smoking prevalence rates back through 1954. Since the HIS data did not provide age-specific prevalence rate estimates for the age groups 80–84 and ≥85 during the earliest time periods, we used the rates based on our estimates for 1975. The error induced by this should have little impact, since few people were in these age groups.

Table 1. Estimated prevalence of current smokers according to age and sex in the United States, 1966–1975

Sex	Age (yr)	1966		1970		1975	
		Survey*	HIS†	Survey	HIS†	Survey	HIS†
Males	20–24	61.9	56.2	49.8	52.4	41.3	46.5
	25–34	59.9	56.2	46.7	52.6	43.9	50.4
	35–44	59.0	57.4	48.6	53.0	47.1	47.2
	45–54	53.8	54.3	43.1	51.1	41.1	47.3
	55–64	47.7	44.2	37.4	42.0	33.7	41.6
	≥65	27.8	25.9	22.8	28.1	24.2	27.9
Females	20–24	49.2	43.1	32.3	38.7	34.0	37.5
	25–34	45.1	43.2	40.3	43.0	35.4	39.8
	35–44	40.6	40.9	38.8	39.6	36.4	39.9
	45–54	42.0	36.5	36.1	36.9	32.8	36.4
	55–64	20.6	21.6	24.1	26.9	25.9	30.1
	≥65	7.6	8.0	10.2	11.4	10.2	15.1

*From (*41*); separate surveys were done in 1966, 1970, and 1975.
†Estimated from 1978–1980 HIS as described in text.

Figure 1 shows a steady decrease in the sales-weighted average cigarette tar content from 37.5 mg in the mid-1950s to 14 mg in 1980, a drop of over 60%. The estimated number of cigarettes sold to males peaked between 1960 and 1965 and has declined steadily since then, whereas the estimated number sold to females has risen over this period. When fitting the model in equation 3, we used 5-year averages of the average tar content or of the product of average tar and number sold. Because changes in carcinogenic exposure are not reflected immediately in changing cancer mortality, we examined possible lag periods between our exposure measures and mortality when fitting the regression model in equation 3. Information on the average tar content of cigarettes sold before 1954 is not available. Since filter cigarettes were originally introduced in the mid-1950s, one assumption is that tar content underwent little change before this time (Warner K: personal communication). Therefore, we assumed the pre-1954 average cigarette tar content to be the average of the 1954–1958 levels, 36.6 mg. On the basis of minimizing the deviance as a measure of goodness-of-fit, we concluded that the best exposure regressor variable is the product of average tar content and number of cigarettes sold, lagged for 24 years. Peace (*32*) found a 21-year lag when correlating overall lung cancer mortality with cigarette tobacco sales by weight in England and Wales during 1880–1983. However, his analysis was not adjusted for age and birth cohort.

In addition to changes in tar content of cigarettes, there have been other changes that probably have affected lung cancer patterns. Changes in air pollution and occupational exposure head the list. We judge these likely to be very small in comparison to cigarette smoking. The relative risk of occupational exposures that might serve as an upper bound for the effect of environmental carcinogens is on the order of 1.4–3.2 (*33*), and these apply to small proportions of the population, leaving a small attributable risk. Others have suggested a minor role for pollutants (*4*), and the evidence from time trends in nonsmokers does not substantiate any temporal effect in environmental carcinogens (*34*). Finally, recent evidence from a large case-control study in Western Europe shows substantial reductions in lung cancer incidence attributable to lower tar cigarettes (*35–37*).

To assess whether separate regression coefficients were needed for males and females and for different age groups, we compared the fit of various models using an analysis of deviance (*38*). Our analysis indicated that the slope of the average tar content × number cigarettes sold exposure variable differs by both sex and age. A statistical test of equal slopes for males and females yields a one degree of freedom chi-square value of 37.6, while a test for equal slopes for under age 50 and ≥50 yields a value of 155, both highly significant ($P < .001$). We examined other age group categorizations and found the under/over 50 to give the best fit. As shown in tables 2 and 3, females have a larger slope than males and the under-50 group has a larger slope than the over-50 group. These differences are consistent with surveys beginning in the late 1960s that have shown that males and older persons are more likely to continue to smoke higher tar cigarettes (*39*). Therefore, decreases in tar levels would be

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expected to have a greater effect on lung cancer among females and younger persons. Thus our final model that we fit to male and female lung cancer mortality is

$$\log(r_{ij}) = \begin{cases} A_i + B_1 X_j + C_{I-i+j} & i \leq 4 \\ A_i + B_2 X_j + C_{I-i+j} & i \geq 5 \end{cases} \quad [4]$$

where B_1 is the regression coefficient for ages 30–49 and B_2 is the coefficient for ages ≥50.

Parameter estimates of the age, period, and birth cohort effects for males and females are given in tables 2 and 3,

Table 2. Parameter estimates from fitting model in equation 4 to male lung cancer mortality

Age (yr)		Birth cohort	
30–34	−12.92	1869–1877	0.13
35–39	−11.77	1874–1882	0.37
40–44	−10.79	1879–1887	0.64
45–49	−9.95	1884–1892	0.96
50–54	−9.01	1889–1897	1.22
55–59	−8.43	1894–1902	1.42
60–64	−7.91	1899–1907	1.56
65–69	−7.54	1904–1912	1.64
70–74	−7.25	1909–1917	1.72
75–79	−7.08	1914–1922	1.79
80–84	−6.98	1919–1927	1.85
≥85	−7.01	1924–1932	1.92
		1929–1937	1.87
Slope of average tar × No. sold		1934–1942	1.75
		1939–1947	1.52
Age 30–49 yr	2.24×10^{-3}	1944–1952	1.21
Age ≥50 yr	0.92×10^{-3}		

Table 3. Parameter estimates from fitting model in equation 4 to female lung cancer mortality

Age (yr)		Birth cohort	
30–34	−13.42	1869–1877	−1.20
35–39	−12.20	1874–1882	−1.04
40–44	−11.19	1879–1887	−0.92
45–49	−10.36	1884–1892	−0.77
50–54	−9.55	1889–1897	−0.59
55–59	−8.95	1894–1902	−0.33
60–64	−8.40	1899–1907	−0.01
65–69	−7.93	1904–1912	0.36
70–74	−7.52	1909–1917	0.75
75–79	−7.21	1914–1922	1.07
80–84	−6.96	1919–1927	1.29
≥85	−6.77	1924–1932	1.50
		1929–1937	1.60
Slope of average tar × No. sold		1934–1942	1.58
		1939–1947	1.49
Age 30–49 yr	5.38×10^{-3}	1944–1952	1.29
Age ≥50 yr	3.28×10^{-3}		

respectively. The male lung cancer mortality rate peaks for the cohort born around 1928, while the rate for females attains a peak for the cohort born around 1933. Since the age and cohort parameters are unique up to an additive constant, we adjusted the age parameters to reflect the age-adjusted mortality rates among nonsmokers (*34*). This was done so the model would predict what the effect of eliminating smoking would be to attain nonsmoker mortality rates.

Day and Charnay (*23*) suggested interpreting the cohort parameters as reflecting the number and type of cigarettes a cohort becomes habituated to smoking when young. To examine this interpretation, figures 2 and 3 compare the time patterns of the sex-specific cohort parameter estimates with the age-specific cigarette smoking prevalence estimates among males aged 20–24 and females aged 30–34 for different birth cohorts. Because the prevalence of smoking for a cohort peaks around these ages, this age-specific prevalence is hypothesized to represent a measure of smoking habits by birth cohort, which becomes translated into the cohort parameters in our mortality model. The age at which this prevalence reaches a peak has changed over the years. For cohorts born around 1900, the peak prevalence was reached around age 30 for men and age 45 for women. More recent cohorts have shown a peak at 20–24 for males and 25–29 or 30–34 for females.

Both figures show that each set of estimated cohort parameters for lung cancer mortality exhibits a pattern quite similar to that of our cohort smoking behavior index. The time patterns of the cohort parameters and cohort smoking index exhibited by the females are very similar to one another (correlation coefficient of 0.99), while the pattern of the male cohort smoking index appears less regular than the female pattern (correlation of 0.83). We hypothesize that the male pattern has been affected by the Depression, reducing the smoking index for cohorts born from 1905 to 1920. These figures indicate that our proposed cohort smoking index provides a good representation of the cohort parameters in our age-period-cohort model, and this correlation will be used for the projections in the following section.

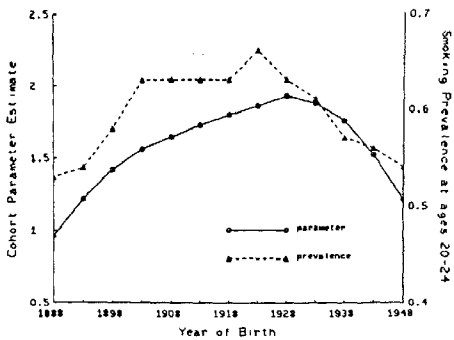

Figure 2. Comparison of estimated cohort parameters and prevalence of smoking at ages 20–24 for U.S. white males.

Basis for projections. To make projections of lung cancer mortality, our age-period-cohort model requires projections of the parameters of the period and cohort factors. Our assumption that the age parameters remain fixed at their estimated values is consistent with our interpretation that they represent the background level of lung cancer risk in a nonsmoking population. Because lung cancer risk is primarily the result of cigarette smoking, our estimates of the future period and cohort factors are based on projections of future

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cigarette composition and consumption. From the model in equation 4, the period parameters are linear functions of the product of average cigarette tar content with the number of cigarettes sold, while figures 2 and 3 show that the cohort parameters can be estimated as functions of the prevalence of smoking among young adults. Therefore, we need to project: (1) the average tar content of cigarettes sold in the United States, (2) the number of cigarettes sold in the United States, and (3) the prevalence of smoking among young adults.

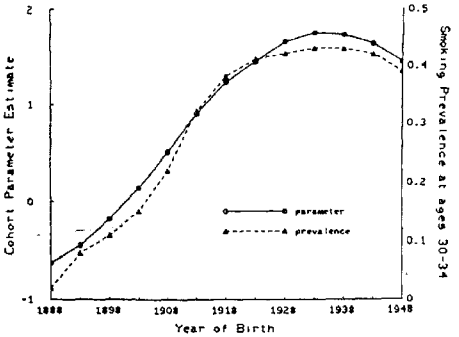

Figure 3. Comparison of estimated cohort parameters and prevalence of smoking at ages 30-34 for U.S. white females.

Projecting tar content in the future is somewhat difficult because the sales-weighted averages shown in figure 1 are a combination of changes in the production of virtually all cigarettes made in the United States, the development of filters and of new low-tar brands in the last three decades, and changes over time in the proportion smoking various types. In addition, the trends in these data are quite strong and almost linear; however, a linear decrease cannot continue unabated, and the point at which one might choose to "level off" these projections is speculative. Surveys have shown that smokers of high-tar (especially unfiltered) cigarettes are generally concentrated among the elderly (*19*), and these individuals will soon die off, creating further declines in the sales-weighted average tar level. In addition, as the proportion of women in the smoking population increases, the market share of high-tar cigarettes will likely further decrease.

For the projections to follow, we assume sales-weighted tar will continue to decrease in a linear fashion until reaching the optimistic level of 5 mg per cigarette and then level off. This linear trend is estimated from the 1972-1981 average tar content values, when the estimated yearly decrease was 0.74 mg. In a second scenario we took the conservative view of leaving the sales-weighted tar constant at 13.22 mg per cigarette, the 1981 value.

A projection of the future number of cigarettes sold in the United States requires projections of future smoking prevalence among all adults and the average number of cigarettes purchased by each smoker. Developing projections for smoking prevalence, we relied on the objectives developed by the NCI for the Year 2000 Project (*40*). The NCI has set a goal of decreasing the smoking prevalence from current levels to 15% of all adults by the year 1990. Our smoking prevalence projections are based on assuming a linear decrease in the age-adjusted (ages ≥15 adjusted to the 1980 population) smoking prevalence from the levels of 40.6% for males and 32.3% for females estimated from the 1978/1980 HIS. To project our exposure index of the tar × number sold per capita, we assume that the average number of cigarettes sold per smoker would remain at the 1980 levels. Therefore, the projected values of our tar × number sold index is the product of the projected tar level, the projected prevalence of smoking, and the number of cigarettes sold to smokers. These projections, along with the values observed in the past, are given in table 4.

Because of our estimated 24-year lag, these average levels during 1934/1938, . . ., 1954/1958 provide the calendar period component of the fitted mortality rates for the periods 1958/1962, . . ., 1978/1982, while the actual and projected levels for the years 1959/1963 through 1999/2003 are components of our mortality rate projections through the period 2023/2027.

As seen in figures 2 and 3, the pattern of fitted cohort parameters in our mortality model is similar to the pattern of smoking prevalence among young adults. Therefore, we use projections of the age-specific prevalence of smoking for males aged 20-24 and females aged 30-34 to estimate future cohort parameters for our mortality projections. We found that the best fitting functional relationship between young adult smoking prevalence and the cohort parameters to be $Y_i = bX_i^2$, where Y_i represents the fitted cohort parameter and X_i represents the smoking prevalence for the ith birth cohort ranging from 1888 to 1948. This relationship assumes no intercept so that as the smoking prevalence

Table 4. Actual and projected 5-year averages of tar × number of cigarettes sold (in 1,000s) per capita

Years	Averages	
	Males	Females
	Actual	
1934/1938	108.9	22.1
1939/1943	145.3	36.0
1944/1948	203.1	58.9
1949/1953	212.8	72.7
1954/1958	207.6	79.6
1959/1963	169.2	72.7
1964/1968	137.9	66.4
1969/1973	113.6	61.2
1974/1978	94.8	57.7
	*Projected**	
1979/1983	59.4	48.1
1984/1988	35.3	31.4
1989/1993	18.0	17.9
1994/1998	14.1	14.1
1999/2003	14.1	14.1

*We assume: (1) tar content to decrease linearly to 5 mg in 1993 and (2) smoking prevalence to decrease linearly to 15% for all adults in 1990.

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decreases to zero the cohort parameters would also go to zero and the age-specific lung cancer mortality risk would become the 1958–1968 nonsmokers' risk as noted in the previous section. The regression for males was estimated by least squares applied to the data in figure 2, which resulted in an estimated slope $\hat{b} = 4.4$. The regression for females was estimated from the 1908–1948 data shown in figure 3 and resulted in an estimated slope of $\hat{b} = 8.2$.

Following the Year 2000 Project objectives, one scenario is that the prevalence of smoking among young adults drops to 15% by the year 2000. Our smoking prevalence projections for males aged 20–24 assume a linear decrease from the 41% observed for those born during 1956–1960 to 15 or 0% for those born during 1976–1980 (being 20–24 in the year 2000). The projections for females aged 30–34 decrease linearly from the observed 39% for those born during 1946–1950. The smoking prevalence projections assuming 15% prevalence by the year 2000 are given in table 5.

Table 5. Projection of smoking prevalence among young adults*

Year of birth	Smoking prevalence†	
	Males	Females
1946–1950	(0.54)	(0.39)
1951–1955	(0.48)	0.33
1956–1960	(0.41)	0.27
1961–1965	0.345	0.21
1966–1970	0.28	0.15
1971–1975	0.215	0.15
1976–1980	0.15	0.15

*Cell entries are smoking prevalence for males of ages 20–24 and females of ages 30–34 by birth cohort; both sexes assumed to have 15% prevalence of smoking by the year 2000 in their respective age groups; as explained in the text, cohort parameters are given by:

$$\text{Males: parameter} = 4.4 \times (\text{smoking prevalence})^2$$
$$\text{Females: parameter} = 8.2 \times (\text{smoking prevalence})^2$$

†Observed prevalence in parentheses.

Projections of mortality. The age-adjusted projections are shown in table 6 and figure 4 for the NCI objectives compared to a "baseline" alternative in which tar content and smoking prevalence are assumed not to change after 1980. For both males and females, but especially for males, the two sets of projected rates for the period 1998/2002 differ very little because of the estimated 24-year lag for the effect of changes in tar content and age-adjusted smoking prevalence. The only changes in our mortality projections in this short time span are due to different cohort effects, and these will affect only the young age groups with low mortality rates before the end of this century. For males, the projected year 2000 age-adjusted rate under the NCI objectives is 68.1 per 100,000, just 0.7% less than the rate of 68.6 per 100,000 for the no-change scenario. The differences in mortality rates projected for the period 2023/2027 between the two scenarios are noticeably larger. The projected rates for males are 43.0 and 28.8 per 100,000 for the no-change and NCI scenarios, respectively, representing a 33% decline due to accomplishing the NCI's smoking objectives. A larger difference is apparent for females for the 2023/2027 period:

Table 6. Actual and projected age-adjusted lung cancer mortality rates per 10^5

Years	Actual rates	
	Males	Females
1958/1962	38.1	5.8
1963/1967	47.3	7.5
1968/1972	57.9	11.1
1973/1977	65.2	15.2
1978/1982	71.0	20.6
	Projected rates	
	Males	Females
	NCI obj.* / No change	NCI obj.* / No change
1983/1987	72.6 / 72.6	25.6 / 25.6
1988/1992	72.9 / 73.0	30.8 / 30.8
1993/1997	71.5 / 71.7	35.4 / 35.6
1998/2002	68.1 / 68.6	38.9 / 39.5
2003/2007	61.3 / 64.6	39.6 / 42.3
2008/2012	52.8 / 58.9	36.2 / 43.2
2013/2017	44.5 / 52.7	32.9 / 42.6
2018/2022	36.1 / 47.0	28.3 / 40.8
2023/2027	28.8 / 43.0	23.4 / 38.8

*NCI objectives: (1) tar content decreases linearly to 5% in 1993, (2) age-adjusted smoking prevalence drops to 15% in 1990, and (3) smoking prevalence in young adults drops to 15% in 2000.

there is a 40% difference in the projected rates, from 38.8 to 23.4 deaths per 100,000.

Varying each of the three elements of the projection model, tar, age-adjusted smoking prevalence, and age-specific prevalence among new smoking cohorts, produces different projection tables for males and females. We examined more conservative projections, for example, tar levels not decreasing below 1982 levels and age-adjusted prevalence not declining below 25% for adults, as well as more liberal projections, including, for example, no new smokers among young adults by the year 2000. For the near term, the period 1998/2002, the differences in age-adjusted

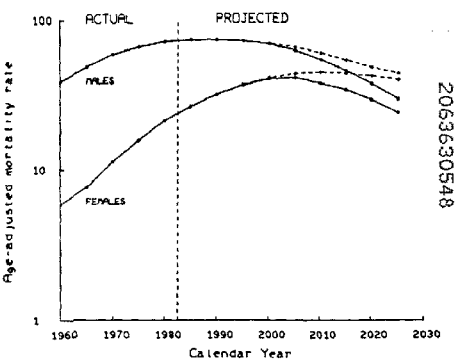

Figure 4. Actual and projected age-adjusted lung cancer mortality rates for U.S. white males and females, 1960–2025. —— = NCI objectives; --- = no change.

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rates are trivial. As the projection horizon lengthens, the differences become more noticeable. However, the rates based on more liberal objectives are similar to the NCI objective projections, illustrating that accomplishment of the NCI objectives (tar declines linearly, smoking prevalence at 15%) would include much of the potential reduction in lung cancer mortality for the next several decades. We considered the more dramatic scenario of a 0% prevalence of smoking by the year 2000 and obtained similar results. For example, under this scenario, the projected male age-adjusted mortality rate for the period 2023/2027 is 27.9 per 100,000, only 3.1% less than the projection of 28.8 based on the NCI objectives. Females show a larger relative decline of 11% from 23.4 deaths per 100,000 to 20.9 in the 2023/2027 period. These detailed age-specific projection tables are available from the authors upon request.

Projections at the age-specific level better illustrate why the rate of decline in the age-adjusted projections is so slight. When the different effects begin to be seen in each of the age groups and how fast these rates drop are crucial to interpreting the plausibility of the projections. As shown for males in figure 5, by the year 2000 only the age groups under 45 are affected by the decrease in new smokers represented by attaining the NCI objectives. For groups older than age 45, changes are not apparent until later. For males aged 55–59, the recent (1978/1982) lung cancer mortality rates are 169 per 100,000. Under the no-future-change model, these are projected to be 109 in the year 2000 and lower still to 80.5 by the year 2025. Therefore, the no-change scenario includes a substantial decline in lung cancer mortality for this younger age group to begin in the near future and to carry through this projection horizon due to changes in tar content and smoking prevalence that have already occurred. Achievement of the NCI objectives would further reduce these rates to 31.2 in 2025. A similar picture is evident for older males. Among the 75–79 year olds, compared to a recent rate of 487, the no-change scenario projects rates of 587 for the year 2000 and 311 by the end year of the projections (2025). The decline in mortality rates for this age group begins about the year 2005, 20 years after the turnaround for the 55–59 year age group. The general age-specific pattern for females is quite similar, but shows a later period of peak mortality rates (fig. 6). For the 55–59 year age group, the peak mortality rate of 79.6 is projected to be in the 1988/1992 period, 5 years later than males. The female rates for this age group for the years 2000 and 2025 are projected to be 69.4 and 56.9, respectively, under the no-change scenario. Attaining the NCI objectives reduces the later projected rates to 13.0 per 100,000.

Discussion

Trends in the United States during the past two decades have shown a dramatic turnaround in smoking prevalence. Because of these trends, changes in lung cancer and other tobacco-related diseases have been eagerly anticipated. Declines in age-specific rates of lung cancer for young ages have been seen recently as a result of lower smoking prevalence among new cohorts and as a result of lower tar content in cigarettes. However, age-adjusted rates of lung cancer mortality have continued to climb for males, although recently there has been a noticeable flattening of these rates. For U.S. females, however, incidence and mortality rates have continued to dramatically increase.

In the present analysis, we have constructed a model to take account of these trends of major public health interest and have provided a framework for projecting rates into the future. The model is based on age-period-cohort modeling, which has been used extensively in cancer epidemiology. In addition to fitting the model to available lung cancer mortality data, we have analyzed recent survey data on cigarette consumption and incorporated these findings into the projection model. This allows the projection of lung cancer rates, providing one is willing to make a set of assumptions about the three key factors that we believe are the major determi-

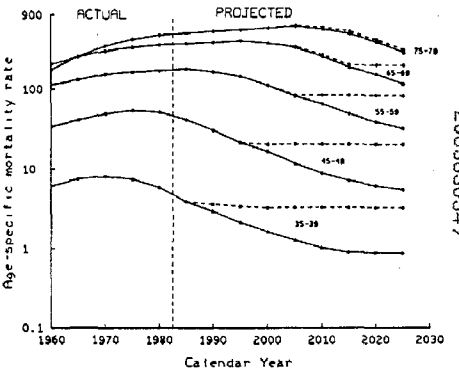

Figure 5. Actual and projected age-specific lung cancer mortality rates for U.S. white males, 1960–2025. —— = NCI objectives; --- = no change.

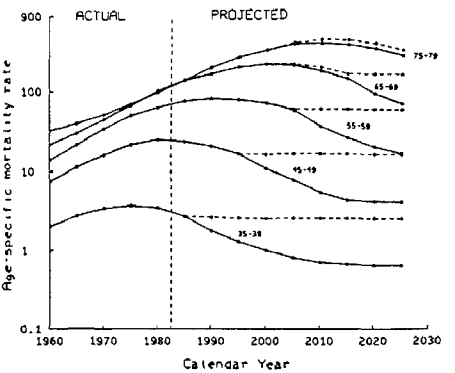

Figure 6. Actual and projected age-specific lung cancer mortality rates for U.S. white females, 1960–2025. —— = NCI objective; --- = no change.

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nants of lung cancer mortality: starting the smoking habit, continued smoking prevalence, and tar content of cigarettes.

Projections of lung cancer rates in the absence of any major changes in these factors show that the age-adjusted rates in males will be relatively flat through about 1990 and will then gradually decline. Mortality patterns for females lag behind those for males, and in the absence of changes, rates are projected to peak about the year 2010. The age-specific peaking for females is only 5 years behind that for males; the age-adjusted rates peak later for females because of their more recent increase in smoking prevalence.

Achievement of objectives for reducing smoking prevalence advocated by the NCI will have little impact on these trends in the very near future. Little material changes can be expected by the year 2000 based on the empirical findings here; however, the longer term impact of the NCI objectives is much more positive. Compared to no changes in smoking prevalence and cigarette tar content, attaining the NCI objectives could reduce the age-adjusted male lung cancer mortality rate by almost 33% by the period 2023/2027 and the female mortality rate could be reduced by over 40%. Assuming attainment of the NCI objectives, we note that the projected age-adjusted rate for males for the period 2023/2027 of 28.8 per 100,000 represents almost a two-thirds reduction of the 1978/1982 mortality rates. Although the rate of 23.4 per 100,000 for females in 2023/2027 is about equal to recent rates, this is a considerable reduction on what would be projected under current trends. Advances in secondary and tertiary prevention represented by screening and treatment might also affect future lung cancer mortality trends, but we have limited our analysis to the future effects of cigarette smoking behavior.

We are somewhat surprised by the intractability of the rates in the near future. However, the empirical fit of the model to the data suggested lagged effects for parameters, which are consistent with previous literature (*32*). Thus reduction in lung cancer mortality rates in the next decade or two will occur only if recent decreases in smoking prevalence continue and efforts to reduce smoking further are adopted throughout the United States.

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Cigarette smoking and male lung cancer in an area of very high incidence

I Report of a case-control study in the West of Scotland

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SUMMARY Altogether 656 male lung cancer cases and 1312 age and sex matched controls were interviewed between 1976 and 1981 in a case-control study of cigarette smoking habits and lung cancer in Glasgow and the West of Scotland, an area with the highest recorded incidence in the world. The relative risk of lung cancer increased significantly for smokers whose consumption was below 20 cigarettes per day but did not rise significantly in those who smoked more than 20 cigarettes per day. Other smoking characteristics such as inhalation and tar yields of brands smoked did not explain this finding. Additionally, the relative risks observed at all levels of cigarette consumption were low in comparison with those in the published literature. By constructing an index of cigarette exposure which included the tar yields of brands smoked, an assessment of the risk of lung cancer in relation to tar exposure independent of amount smoked was derived. Only in smokers of less than 15 cigarettes per day was there a statistically significant reduction in risk of lung cancer associated with lower levels of tar yield.

It is now more than 30 years since the publication of the first definitive epidemiological study by Doll and Bradford Hill on the aetiology of lung cancer in the United Kingdom.[1] None of the geographical areas in which these studies have been undertaken have as high an incidence of lung cancer as the West of Scotland.[2] In 1984, smoking-related cancers were responsible for 54% of all new male cancer cases in the Greater Glasgow Health Board area, and the male lung cancer mortality rate for the area was 158 per 100 000.[3]

This report of a case-control study of cigarette smoking and lung cancer is presented firstly because the relative risk above an average of 20 cigarettes per day does not rise significantly, contrasting with the majority of retrospective case-control studies published since Doll and Hill's original article,[1] and, secondly, because the results are supported by a prospective cohort study carried out at approximately the same period of time, between 1972 and 1984, in an adjacent geographical area which is demographically similar and has a similar male lung cancer mortality rate (156 per 100 000).[3]

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Material and methods

A total of 3125 patients admitted to general and respiratory wards in hospitals within urban West of Scotland were interviewed between January 1977 and May 1981. Potential cases and controls were chosen on the basis of the provisional diagnosis stated on admissions lists. The status as either case or control was subsequently confirmed by checking the final diagnosis for each admission in the Medical Records Department of the hospitals concerned and ultimately in the West of Scotland Cancer Registry.

Any interview with a presumptive diagnosis of lung cancer not subsequently confirmed in the Cancer Registry was discarded. Two controls were matched to each case, matching being made on the basis of age (within five years at the time of diagnosis), sex, and date and place of interview. Matching was made after the final diagnosis of each case and control had been established. The final data presented relate to a total of 656 cases of male lung cancer and 1312 age and sex matched controls.

Histological confirmation was obtained for 77% of lung cancer cases and cytological confirmation for

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18%. The remaining 5% of the lung cancer cases were diagnosed on clinical grounds.

Patients with no major tobacco-related disease as the diagnosis responsible for their current admission were accepted as controls. The major control diagnoses were acute infectious diseases, fractures, and cancers of the colon, rectum, stomach, and prostate and neoplasms of the lymphatic and haematopoetic tissue. No one disease group exceeded 10% of the total number of controls. Both case and control patients were interviewed in hospital by one of two specially trained interviewers. Arrangements were made to ensure, as far as possible, that the interviewers had no knowledge of the diagnosis from members of staff nor access to the case record. A standard questionnaire[4] was used to record and investigate the nature of present and past cigarette use, with particular emphasis on recording changes in the number of cigarettes, smoked, years of usage, and changes in brands during the smoker's lifetime, so as to provide the best possible estimate of exposure during lifetime up to the time of interview.

The age and social class distribution of cases and controls is given in table 1.

The most commonly used statistic in the literature to describe exposure to cigarette tobacco products is the average number of cigarettes smoked per day, and the most frequently used expression of risk, in terms of disease, is the relative risk. Average number of cigarettes per day has been based on the total amount smoked throughout the smoking lifetime. Relative risk has been estimated taking the matching of controls to cases into account.[5]

The questionnaire permitted further measures of cigarette exposure to be described, namely:

1 an estimate of the total number of cigarettes smoked until diagnosis (lifetime packets). This allowed for changes in the number of cigarettes smoked and any periods of stopping smoking to be taken into account.

2 an estimate of the total tar yield to which an individual had been exposed during his smoking lifetime.

Tar yields for the period before 1961 are not known routinely[6] and have been set at the 1961 level. Routine information on the tar yield of cigarettes between 1961 and 1970 is available only from the manufacturers. Since 1971, both the cigarette manufacturers and the Government Chemist have reported tar yields at regular intervals.[7] Using these data, an average tar yield was derived for each brand for each five-year time period, pre–1961, 1961–65, 1966–70, 1971–75, 1976–80. By considering the average number of cigarettes smoked by an individual on a brand basis for each of these intervals, a total tar yield index was constructed.

Thus, reductions in the tar yield of specific brands which have taken place since 1960 and changes between brands of different tar yields have been allowed for.

Ex-smokers have been defined as those who have given up smoking for at least one year. Pipe and cigar only smokers have been excluded from the results. The percentage of cases and controls currently smoking pipes and cigars in addition to cigarettes was 10% and 11% respectively.

Table 1 *Age and social class distribution of cases and controls.*

Age group (years)	*Cases*		*Controls*	
	No	*%*	*No*	*%*
<45	18	2·7	56	4·8
45 –	129	19·7	291	22·2
55 –	264	40·2	472	36·0
65 –	218	33·2	421	32·1
75 +	27	4·1	72	5·5
Total	656		1312	
Median age	60·5		61·2	
Social class*				
I	5	0·8	47	3·6
II	72	11·3	119	9·2
III	315	49·5	567	43·8
IV	103	16·2	309	23·9
V	142	22·3	252	19·5

*19 cases and 18 controls could not be classified.

Results

The relative risk of lung cancer for current smokers of increasing amounts of cigarettes smoked daily is shown in table 2. The relative risk shows a steep linear increase up to 7·6 for an average cigarette consumption of 15–24 cigarettes per day. Cigarette consumption above this level is associated with only a

Table 2 *Average number of cigarettes smoked daily by cases and controls and associated relative risk (ex-smokers excluded).*

Average number of cigarettes smoked daily (present smokers only)	*No of cases*	*No of controls*	*Relative risk*	*95% Confidence interval*
Never smoked*	13	145	1	
1–14	82	205	4·5	2·5– 8·1
15–24	248	361	7·6	4·2–13·8
25–34	76	113	8·6	4·6–16·1
35–49	59	66	9·7	5·1–18·4
50 +	25	26	7·8	3·7–16·4
Total	503	916		

* Never smoked tobacco of any kind.

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small increase in relative risk to 9·7 and falls among those who reported smoking more than 50 cigarettes daily on average.

The dose-response relation, that is, the increase in relative risk with increase in cigarette consumption, for those cases histologically confirmed is shown in figure 1. The sharp rise in risk for those smoking up to 15–24 cigarettes daily is apparent for both squamous and oat cell tumours. Above this level the flattening of the dose-response curve occurs for those with squamous cell cancer and declines (but not statistically significantly) for oat cell cancers. A relatively weak relation for those with adenocarcinomatous tumours is also shown.

Table 3 compares the smoking habits of those cases whose cell type was not distinguished or where no histology was obtained with those where a cell type was distinguished. No statistically significant differences are seen in the percentage of smokers in each category. Thus both groups were amalgamated.

Relative risks for the average number of cigarettes smoked per day, the total number of cigarettes smoked, and the total tar yields are given in table 4. The linear increase in relative risk rises to 11·5 for total tar yield at an average consumption equivalent to 25–34 cigarettes per day and does not appear to rise above this level even if more cigarettes are smoked (see appendix).

Figure 2 shows the relative risk of lung cancer for smokers of 25 cigarettes and more, for those who

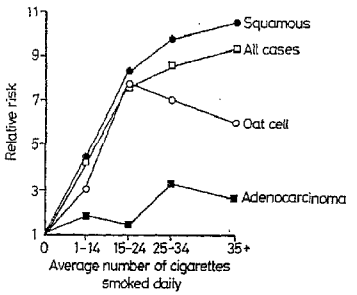

Fig 1 *Relative risk in relation to amount smoked for each cell type.*

Table 3 *Average number of cigarettes smoked daily in cases where the cell type was distinguished and in those where the cell type was not specified.*

Average number of cigarettes smoked daily (present smokers only)	*Cell type specified*		*Cell type not specified*	
	No	*%*	*No*	*%*
Never smoked*	12	3·1	1	0·9
1–14	63	15·9	19	17·8
15–24	193	48·7	55	51·4
25–34	61	15·4	15	14·0
35–49	47	11·9	12	11·2
50+	20	5·1	5	4·7
Total	396		107	

* Never smoked tobacco of any kind.

Table 4 *Relative risks for different measures of exposure.*

Level of exposure *	*Measure of exposure*		
	Average No cigs/day	*Total lifetime packets*	*Total tar yield*
Never smoked	1	1	1
1–14	4·5	3·8	3·7
15–24	7·6	7·0	7·0
25–34	8·6	10·6	11·5
35–49	9·7	12·1	10·5
50+	7·8	8·0	8·9

* See appendix.

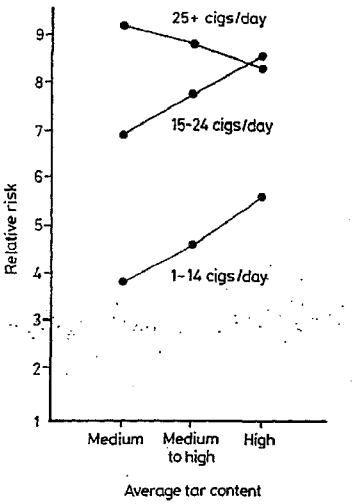

Fig 2 Relative risk in relation to average tar yield for light, medium, and heavy smokers.

smoked 15–24 ciga
smoked 1–14 ciga
exposure to medi
high (23–28 mg/ci
cigarette) yield ci
change significant
more cigarettes pe
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($p=0·07$). Smoker
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Figure 3 shows
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Table 5 *Distributi*
quantities for cases a

Average tar yield	
Low/Medium	
Medium	
Medium/High	
High	
Total cases	
Total controls	

* Percentage of cases sm
low/medium category.
** Percentage of controls
low/medium category.
Cases: $\chi^2_5 = 4·1$, $p = 0·6$
Controls: $\chi^2_5 2·7$, $p = 0·8$

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smoked 15–24 cigarettes per day, and for those who smoked 1–14 cigarettes per day in relation to their exposure to medium (17–22 mg/cigarette), medium/high (23–28 mg/cigarette), and high tar (>28 mg/cigarette) yield cigarettes. The relative risk did not change significantly ($p=0.7$) for smokers of 25 and more cigarettes per day regardless of the tar yield to which they were exposed. For smokers of 15–24 cigarettes per day, the relative risk fell as tar exposure decreased but this fall was not statistically significant ($p=0.07$). Smokers of 1–14 cigarettes per day also showed a decrease in relative risk with decreasing tar exposure. This reduction in relative risk was statistically significant ($p=0.04$).

Table 5 shows the average tar exposure in relation to the quantity of cigarettes smoked by the cases and controls. The percentage of those with high tar exposure among heavy smokers is similar in cases and controls.

Table 6 presents the reported inhalation of smokers in relation to the quantity of cigarettes smoked for both cases and controls. Smokers of less than 15 cigarettes per day seem less likely to be deep inhalers in contrast to the heavier smoking categories. Over 40% of smokers who smoked 25 or more cigarettes per day said they inhaled deeply.

Figure 3 shows the relative risk of lung cancer for the 140 cases and 350 controls who stopped smoking completely for periods ranging from one to 20 years relative to their average consumption before stopping. The pattern of declining risk with stopping smoking is similar for each group of smokers (the first point on fig 3 shows the relative risk of present smokers as in table 2). Only those who reported stopping smoking for at least five years or more show a decline in relative risk.

Table 5 *Distribution of tar yield for smokers of different quantities for cases and controls (present smokers only).*

Average tar yield	*Average No of cigarettes per day*				*Total*
	1–14	*15–24*	*25–34*	*34+*	
Low/Medium	0·0*	0·0	5·0	0·0	4
	1·0**	0·6	0·9	0·0	5
Medium	13·4	10·7	12·5	13·1	58
	15·6	17·9	14·2	12·1	123
Medium/High	80·5	85·2	76·2	83·3	405
	80·0	77·3	80·5	93·5	611
High	6·1	4·1	6·3	3·6	23
	3·4	4·1	4·0	4·4	31
Total cases	82	248	76	84	490
Total controls	205	361	113	92	771

* Percentage of cases smoking 1–14 daily whose average tar yield is in the low/medium category.

** Percentage of controls smoking 1–14 daily whose average tar yield is in the low/medium category.

Cases: $\chi^2_5 = 4.1$, $p = 0.65$
Controls: $\chi^2_5 = 2.7$, $p = 0.85$

Table 6 *Inhalation patterns for smokers of different quantities for cases and controls (present smokers only).*

Depth of inhalation	*Average No of cigarettes smoked daily*				
	1–14	*15–24*	*25–34*	*34+*	*Total*
Non-inhaler	9·5*	4·3	5·8	7·1	24
	9·8**	2·5	3·6	3·3	36
Slight	18·1	11·9	5·8	6·3	60
	19·1	14·0	5·4	3·3	98
Moderate	54·3	50·5	48·1	37·5	245
	52·0	48·9	48·2	45·1	376
Deep	18·1	33·3	40·4	49·1	156
	19·1	34·6	42·9	48·4	255
Total cases	82	248	76	84	490 (3 nk)
Total controls	205	361	113	92	771 (6 nk)

* Percentage of cases smoking 1–14 cigarettes daily who claim to be non-inhalers.

** Percentage of controls smoking 1–14 cigarettes daily who claim to be non-inhalers.

Cases: $\chi^2_3 = 34.0$, $p < 0.001$
Controls: $\chi^2_3 = 56.0$, $p < 0.001$

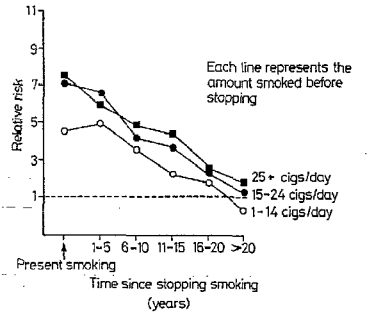

Fig 3 Relative risk in present smokers and ex-smokers according to time since stopping smoking and amount smoked before stopping.

Discussion

The major finding in this study is the steep increase in the relative risk of lung cancer observed in West of Scotland smokers with an average consumption of

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1–14 and 15–24 cigarettes daily, compared with the small increase in relative risk in smokers with a higher average daily consumption (table 2). This is at variance with the majority of the literature which describes a steady increase in relative risk above an average consumption of 20 cigarettes daily.

The validity of the findings in this study is supported by the following:

1 The procedures followed in this study are accepted as current practice in the design of case-control studies.[8] The median age of cases interviewed in the study was younger than in the West of Scotland generally. The control diagnoses were spread over a wide spectrum of non-smoking related diseases with no single control disease exceeding 10% of the total. Although a period of five years was allowed in matching the age at diagnosis of cases and controls, 82·5% fell within three years. The distribution of cell types was similar to that in previous studies although the rate of histological confirmation was somewhat lower.

2 The questionnaire used in this study has been used in many studies of smoking and disease over the past 30 years. Some 50 interviews were repeated by chance during the course of the study. Of these, 48 gave answers regarding cigarette consumption, which, when allocated to smoking exposure categories, were the same as previously given.

3 Variation between interviewers and the quality of the interviews conducted could be closely monitored throughout the study as only two interviewers were responsible for 95% of the interviews. Considerable care was also taken to ensure that they had no knowledge of the diagnosis.

4 The majority of the well known epidemiological associations of cigarette smoking and lung cancer can be reproduced using the data collected in this study; a decrease in relative risk in ex-smokers after five years since stopping[9] (fig 3); squamous and oat cell tumours associated with the highest levels of relative risk whereas adenocarcinomas showing only a minor association with cigarette smoking[10 11] (fig 1); a significant positive association between depth of inhalation and average daily consumption of cigarettes.[12]

The results of this study raise three main questions. Firstly, is the small increase in relative risk in smokers with a high average consumption due to under-reporting of cigarette smoking practice? Secondly, are the cigarette smoking habits of cases and controls different in terms of the type of cigarettes smoked and inhalation, particularly at the higher levels of cigarette consumption? Thirdly, is the proportion of lung cancer patients who are non-smokers different from that in other studies?

With increasing public awareness of the harmful effects of cigarette smoking, individuals, and cases particularly, may have under-reported their level of cigarette consumption, especially those at higher levels. However, in this study the proportion of heavy smokers among the cases (ie, the proportion of individuals who smoke more than 25 cigarettes per day) is larger than in most quoted case-control studies which have resulted in steadily increasing relative risks with increasing dose. The proportion of heavy smokers among the controls in this case-control study not surprisingly also exceeds that in the apparently healthy West of Scotland population sampled in the same period of time.[13] These factors both suggest that under-reporting of cigarette consumption is not a serious bias in this study.

The flattening of the dose-response relation could also have been explained if, among heavy smokers, cases were smoking lower tar cigarettes or inhaling less than controls. However, table 5 shows remarkable similarity between the tar exposure of cases and controls in each category of cigarette smoking with no significant differences detected, and table 6 shows no differences in inhalation between cases and controls.

The possibility also exists that average number of cigarettes per day does not provide an adequate estimation of total dose although this has often been used in the literature. Total lifetime packets, which incorporates the number of years of smoking, and total tar yield also produce a flattening of the dose-response relation at the higher levels of exposure.

Total tar yield is probably the best measure of exposure statistically. There was no increase in relative risk for smokers of 25 cigarettes per day and above whether they smoked high, medium/high or medium tar cigarettes. An increase in relative risk was present for smokers of 15–24 cigarettes per day for increasing levels of tar exposure but the increase in risk was not statistically significant. Only those who smoked 1–14 cigarettes per day showed a statistically significant reduction in relative risk as tar exposure declined from high to medium.

Thus, in an area of exceptionally high lung cancer incidence, there is a lack of increase of the relative risk of lung cancer at higher levels of cigarette smoking. We have been unable to explain this observation on the basis of confounding bias or artefact.

The low level of relative risk found at all levels of cigarette consumption coupled with the small increase in relative risk observed at the highest levels of smoking represent a paradox for an area with such a very high rate of lung cancer.

The existence of a higher than average proportion of heavy smokers in the West of Scotland population would not seem therefore sufficient by itself to be responsible for the high lung cancer rate. Thus the question of additional susceptibility to lung cancer in

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the local population is raised.

The finding of case-control studies are considerably enhanced if supported by prospective cohort studies. The accompanying paper[13] attempts to place the findings of this study in the context of a prospective cohort study of 7055 West of Scotland men with known smoking habits followed for 10½ years.

The data collection phase of this study was undertaken with the financial support of and under contract to the National Cancer Institute, Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, USA, as part of their Smoking and Health Program. Contract No. NO1-CP-05646.

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Statistical appendix

The validity of the indices of exposure to tobacco used in this paper has been examined by considering the contribution each makes to the statistical model of the dose-response relation. This is measured by the 'goodness-of-fit' statistic. If the use of past quantity smoked and historical tar data had been so unreliable as to be meaningless, increased random variation would have been introduced into the indices and no statistically significant improvement in 'goodness-of-fit' would have been apparent. As it was, the index 'lifetime packets' produced a better fit to the model of the dose-response relation than 'average number of cigarettes per day'. However, the best fit was achieved using the index 'total tar yield'.

Index	*Goodness of fit*	*Improvement in fit* (χ^2)*	*p value*
Null	1447		
Average number of cigarettes/day	1337		
Lifetime packets	1317	13·8	<0·001
Total tar yield	1306	18·1	<0·005

* Improvement in fit is expressed relative to the model using average number of cigarettes/day as the measure of exposure.

In order to compare the way in which the relative risk for each measure of exposure changes as the level of exposure increases, it is necessary to define a standardised scale for level of exposure (in the same manner as standard age groups are defined for the 'world standard' population). This has been achieved by defining boundaries in such a way that *an equal proportion of controls* is contained within a category for each measure of exposure. The choice of boundaries has been set to match those used for 'average number of cigarettes per day', this being a scale which is easily conceptualised and which appears most frequently in the literature.

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Smoking and Lung Cancer: Risk as a Function of Cigarette Tar Content[1]

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The hypothesis of reduction in lung cancer risk associated with the adoption of low-tar cigarettes was examined in a subset of subjects from a population-based, case–control study of incident primary lung cancer among New Jersey white men. Risk was related to time-weighted average tar levels of cigarettes smoked in 1973–1980. Unadjusted estimates of risk were significantly low for the lowest tar (<14 mg cig) smokers [odds ratio = 0.53 (0.29,0.97)] compared with the highest (21.1–28 mg/cig). However, adjustment by age and total pack-years rendered the risk reduction insignificant. Of note was the finding that cases who smoked low-tar cigarettes compensated for reducing tar by *increasing* the number of cigarettes they smoked by almost half a pack per day from the years 1963–1972 to 1973–1980, while in the same period controls and high-tar cigarette smoking cases did not increase the numbers smoked. © 1988 Academic Press, Inc.

INTRODUCTION

Cigarette smoking is generally recognized as the primary cause of lung cancer (23–25). Tar, the total dry particulate component of smoke, is a complex mixture of hundreds of substances. There is a body of information classifying these tar compounds as initiators, promoters, cocarcinogens, and so on, and increased consensus as to how these molecules act (28, 31). As to the general conclusion that cigarette tar constituents increase cancer risk, there is no dispute (25).

The quantity of tar per average cigarette marketed in the United States has been declining steadily over three decades for two reasons. The mix of product purchased by the smoking public has shifted, first as filter cigarettes became prevalent in the 1950s, and subsequently as companies introduced new brands to compete for the perceived "low-tar" market. Also, tar reductions have occurred as manufacturers reformulated cigarette brands continuously available from before 1950 to the present. Before 1953, the average tar content of cigarettes was approximately 35 mg each. By 1962, tar in nonfilter cigarettes had declined to about 30 mg each and filters to 22 mg. After another decade, non-filters tested at 27 mg and filters at 17–18 mg. In 1980, non-filters averaged 24 mg and filters only 11 mg.

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Therefore, one might hypothesize some corresponding, measurable impact of this decreasing tar content on lung cancer incidence or risk. This may be phrased in one of two ways: (a) is there decreased lung cancer risk for persons who smoke low-tar cigarettes exclusively; and (b) is present smoking of lower-tar cigarettes, after some term of smoking higher-tar ones, associated with decreased lung cancer risk? We have investigated the latter using data from a population-based incident lung cancer case–control interview study of white men from six areas of New Jersey.

METHODS

All incident white male lung cancer cases diagnosed during the period of September 1980 to October 1981, and occurring in six previously noted high-mortality areas of New Jersey (21), were identified. Cases were ascertained via a rapid reporting system established between the New Jersey Department of Health and local hospital pathology departments, by regular review of hospital pathology logs, and by monitoring the State Cancer Registry and death certificate files. Health Department physicians reviewed pathology reports, along with supporting medical records as required, in order to verify a diagnosis of primary lung cancer. Only histologically confirmed cases were retained for study.

Population-based controls were selected using two procedures. Controls for directly interviewed cases were selected from a random sample of men with New Jersey motor vehicle licenses. This sample was frequency matched to cases by geographic area, race, and 5-year age group. Controls for deceased or incapacitated cases were selected from state death certificate files, and were individually matched to cases by area, race, age, and closest date of death (or date of death nearest the date of diagnosis, for incapacitated cases). Certificates indicating lung cancer or any other respiratory disease as an underlying or contributory cause of death were excluded.

Of the 1,084 white male lung cancer cases eligible for the study, interviews were successfully completed for 763 (70.4%), 429 with self-respondents and 334 with next-of-kin (308 first-degree relatives, 26 more distant). Reasons for noninclusion were late ascertainment (6.9%), insufficient time after death to allow the waiting period required by the Institutional Review Board before contacting next-of-kin (2.1%), physician refusal (4.2%), untraceable respondent (4.2%), respondent refusal (10.8%), and poor-quality interviews (1.4%). Of the 1,415 white male controls identified, interviews were successfully completed with 900 (63.6%), 564 with self-respondents and 336 with next-of-kin (318 first- degree relatives, 18 more distant). Reasons for noninclusion were untraceable respondent (9.0%), respondent refusal (24.7%), and poor-quality interviews (2.8%).

All interviews of subjects or their next-of-kin were conducted in person by field staff experienced in large-scale epidemiologic studies. The modular questionnaire included sections on demographic factors, residential history, personal and familial medical history, history of cigarette, pipe, and cigar smoking, smoking by other household members, occupational history (20), and dietary history (30).

In the cigarette use section of the questionnaire, a smoker first was asked to recall the years in which he smoked cigarettes for any period 6 months or longer.

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Second, he was asked to recall the brands of cigarettes he smoked during each period, the specific years in which he smoked each brand, the number of cigarettes of each brand smoked per day, and the depth of inhalation for each. The interviewer probed for any changes in number per day of a particular brand; a change greater than 10 per day generated a new data entry. The sequence of temporal episodes yielded the summary measures of age started smoking cigarettes, years actually smoked, and years since cessation (if any). The collection of brand name and intensity records for each episode yielded a lifetime intensity measure, or average number of cigarettes smoked per day. A total exposure measure, lifetime packyears, was calculated from the intensity and duration measures. The tar content per cigarette for any brand in any year was determined from historical estimates (22, 24) and test data (4, 5).

Time-weighted average tar levels were calculated for the interval 1973–1980. This period was selected because (a) precise figures for tar content of all domestically produced cigarettes are available; (b) except for the last years of the interval, 1979 and 1980, when ultra-low-tar cigarettes became available, this period did not show so sharp a decline in tar content as the two previous decades; and (c) this proximal portion of the smoking history was assumed to be recalled more accurately by both self- and next-of-kin respondents. We have included smokers with complete brand-specific smoking histories who smoked continuously throughout the interval 1973–1980. Smokers who had quit during the interval were excluded, as were those who stopped prior to 1973.

We compared frequencies of exposure to different 1973–1980 tar levels between cases and controls using the Mantel–Haenszel summary odds ratio (15) with test-based 95% confidence limits (16). Strength of trend was tested by Mantel's method (14), heterogeneity of the odds ratio among sample subgroups was estimated by the method of Breslow and Day (1), and significance of the difference of means by the t test (19). We adjusted for lifetime characteristics of smoking using intensity, duration, intensity and duration simultaneously, or packyears. We examined further possible confounding by respondent type, study area, age at diagnosis, level of education, ever/never smoked pipes and/or cigars, consumption of vegetables, and employment in high-risk occupations (20). We used multiple logistic regression models for simultaneous adjustment by packyears and other potential confounders (1, 18).

RESULTS

Of the 763 cases and 900 controls in the study sample, 13 cases and 142 controls never smoked any tobacco product and 727 cases and 671 controls smoked cigarettes for at least 6 months for an overall crude odds ratio of 11.8 (7.4, 18.9). The other tobacco users, 23 cases and 87 controls, smoked only pipes and/or cigars, and had a crude odds ratio of 2.89 (1.42, 5.88).

Restriction of the sample to those with complete smoking histories reduced the number of cigarette smokers from 1,398 (Table 1, All) to 1,142 (Table 1, subset A), but made little difference in the distribution of cases and controls by age and by summary smoking measures. Differences between cases and controls for the summary smoking measures were significant and similar in magnitude in the total

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TABLE 1

CHARACTERISTICS OF CASE AND CONTROL CIGARETTE SMOKERS, WITH SUCCESSIVE RESTRICTIONS OF SAMPLE, NEW JERSEY WHITE MEN, 1980–1981[a]

	All cigarette smokers		Subset A: all with complete smoking histories		Subset B: all in A who smoked throughout 1973–1980	
	Cases	Controls	Cases	Controls	Cases	Controls
Number of subjects	727	671	583	559	373	247
Age, years	64.7	64.4	64.2	64.1	62.1	62.5
Intensity, cigarettes/day	29.3	24.7*	29.4	23.8*	29.8	23.8*
Duration, years	43.5	36.4*	42.6	35.7*	46.4	45.0
Smoking cessation, years	4.7	10.1*	5.0	10.5*	0.043	0.061
Age began smoking, years	16.5	17.6*	16.6	17.6*	15.7	16.9*
Total exposure, packyears	64.4	46.2*	63.0	43.7*	68.8	53.2*

[a] Mean value.
* $P < 0.05$ for difference between means of cases and controls.

sample and in the first subset; there were no case–control age differences. Further restricting the sample to those who smoked throughout the interval 1973–1980 (Table 1, subset B) reduced the mean number of years since cessation to nearly zero, and erased the previously noted case–control difference for duration. The remaining analyses refer only to these 620 subjects.

Due to the reduction in tar content of both non-filter and filter cigarettes, the average tar level of the cigarettes smoked during 1973–1980 did not exceed 28 mg, 80% of the pre-1953 level of 35 mg tar per cigarette. The median tar level for the 373 cases was 18.6 mg/cig and for the 247 controls was 18.2 mg/cig.

Four tar-level groups were selected. The frequency distribution of tar levels for controls showed three peaks, one consisting of the subjects smoking cigarettes with 21–28 mg tar, another consisting of the very-low-tar smokers, at 14 mg or less, and the bulk of the smokers in a broad middle group that we divided just above the modal value of 17.5 mg/cig. Table 2 shows that the unadjusted odds ratio for subjects at the lowest tar level, relative to subjects at the highest level, was significantly lower than 1.0. There was a significant trend (one-sided $P = 0.04$) in odds ratios with increasing tar. However, taking cognizance of the subject's lifetime smoking behavior increased the odds ratio for the lowest-tar group so that it was no longer significantly different from the reference level. Controlling for packyears resulted in the greatest shift of the odds ratio toward 1.0.

We examined possible differences in the packyear-adjusted tar-level odds ratios by respondent type. Although self-respondents showed a more consistent pattern in odds ratios with increasing tar, the trend was not significant; none of the odds ratios was significantly different from the reference level, and there was no significant heterogeneity by respondent type at any tar level. The packyear and respondent type-adjusted odds ratios were almost identical to those previously shown in Table 2 for adjustment by packyears alone.

We made similar comparisons of age-specific odds ratios, because the association with tar might be more pronounced in younger persons, with a shorter early

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TABLE 2

ODDS RATIOS FOR LUNG CANCER ASSOCIATED WITH TAR LE L OF CIGARETTES SMOKED IN 1973–1980, ADJUSTED BY OTHER LIFETIME MEASURES OF IGARETTE CONSUMPTION[a,b]

	Tar level, 197		1980, mg/cigarette	
	≤14.0	14.1–17.5	17.6–21.0	21.1–28.0[c]
Number of cases/controls:	25/28	131/91	78/45	139/83
Unadjusted odds ratio	0.53 (0.29,0.97)	0.86 (0.59,1.26)	1.04 (0.66,1.64)	1.00
Adjusted by intensity[d]	0.61 (0.33,1.12)	1.01 (0.68,1.51)	1.16 (0.72,1.86)	1.00
Adjusted by duration[e]	0.58 (0.32,1.07)	0.89 (0.60,1.32)	1.05 (0.65,1.67)	1.00
Adjusted by intensity and duration[f]	0.61 (0.32,1.13)	1.04 (0.70,1.56)	1.21 (0.75,1.96)	1.00
Adjusted by packyears[g]	0.71 (0.37,1.35)	1.06 (0.71,1.59)	1.19 (0.73,1.93)	1.00

[a] Sample includes smokers with complete smoking histories who smoked throughout 1973–1980 (subset B in Table 1).
[b] Mantel–Haenszel estimate of odds ratio (95% confidence li ts).
[c] Reference group.
[d] As <20 cig/day, 20–29, 30–39, 40–49, 50+.
[e] As <30 years, 30–39, 40–49, 50+.
[f] Intensity as for [d], duration <40 years, 40+.
[g] As <20 packyears, 20–39, 40–59, 60–79, 80–99, 100+.

history of smoking the available high-tar cigarette : There was little consistent variation by age; the youngest age quartile showed pattern in risk with increasing tar. The packyear and age-adjusted odds ratios ere again almost identical to those shown in Table 2, except that the odds rat for the lowest-tar group increased further to 0.85 (0.42, 1.75).

Because vegetable consumption is associated wi lung cancer most strongly in current and recent ex-smokers (30), we were co erned that the effect of diet might mask an association with tar. Therefore w calculated packyear-adjusted odds ratios by tar level and vegetable consumpti n, relative to subjects in the highest-tar/lowest vegetable consumption group. he association with tar was apparent only in the group with highest vegetable nsumption, among whom the lowest-tar subgroup showed a significantly low od ratio of 0.24 (0.07, 0.83). The trend in odds ratios with increasing tar in this hi vegetable group had a one-sided P value of 0.06. The result of adjustment packyears and by vegetable consumption simultaneously was no different tha obtained from adjustment by packyears alone; there was little consistent overa association with tar. Furthermore, adjustment by tar level and packyears did n change the significant inverse association of lung cancer with vegetable consum tion (32).

Adjustment by other potential confounders, for xample degree of inhalation or education in addition to packyears, did not appre bly change any of the patterns in odds ratios previously described. The same w true of the logistic regression analysis. Examination of different combinations f factors suggested that signif-

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icant contributors to the predictive power of the model were packyears, age, vegetable consumption, and employment in high-risk occupations. Inclusion of these resulted in odds ratios of 0.83 (0.43, 1.60), 1.11 (0.74, 1.67), 1.28 (0.78, 2.10), and 1 for the four tar levels.

It is possible that smokers, although receiving some unspecified amount of risk reduction by using lower-tar cigarettes, could negate that benefit by smoking more cigarettes. We compared, for cases and controls at each tar level, differences between the numbers of cigarettes smoked per day in the interval 1973–1980 and the intensity in the immediately preceding decade (Table 3). Overall, cases increased their consumption more than controls did, although this difference was not significant. Among cases, there was a consistent increase in intensity with decreasing tar, whereas among controls there was no consistent pattern. The difference between case and control changes in consumption was significant for the lowest-tar group. We further attempted to localize this difference to a particular tar level of cigarettes smoked in 1963–1972. The only significant difference in changes in numbers of cigarettes per day between cases and controls was that for smokers who were in the lowest-tar category in *both* 1963–1972 and 1973–1980. These 19 cases increased their consumption by 9.3 cigarettes per day between the two time periods, whereas the 13 controls showed no change whatever in consumption.

DISCUSSION

In addressing the question of whether smoking of low-tar cigarettes is associated with decreased lung cancer risk, the cardinal problem is one of definition: what is a low-tar cigarette? The way this problem has been approached by many is to differentiate cigarettes by a proxy variable, whether they are filtered or not (2, 12, 29, 30). While the amount of tar in filter cigarettes as a class probably has never been greater than that in nonfilter cigarettes, it should be noted that filter cigarettes initially available in the early 1950s had higher tar content than plain tip ones today; "high" and "low" are relative terms.

An alternative approach used by others (8, 10, 13, 26), and with which we

TABLE 3

MEAN DIFFERENCE BETWEEN NUMBER OF CIGARETTES SMOKED PER DAY IN 1973–1980 AND IN 1963–1972, BY CASE–CONTROL STATUS, AND BY TAR LEVEL IN 1973–1980[a,b]

	Tar level, 1973–1980, mg/cigarette				
	≤14.0	14.1–17.5	17.6–21.0	21.1–28.0	All
Cases	+6.8* (25)	+2.1 (130)	+0.7 (78)	0.0 (139)	+1.4 (372)
Controls	−1.1 (27)	+0.8 (89)	+1.3 (45)	−0.1 (83)	+0.4 (244)

[a] Difference = No. cigs/days (1973–1980) − No. cigs/day (1963–1972). No. of subjects in parentheses.

[b] Total No. of subjects = 616; 4 subjects who smoked throughout 1973–1980 did not smoke throughout 1963–1972.

* $P < 0.05$ for difference in mean difference between cases and controls.

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associate ourselves in this study, is to derive a scale from cigarette tar-content information. Although some controversy surrounds the Federal Trade Commission's methods and published lists of smoke component measures, the ordering of particular brands with respect to others is likely to be correct, and *per extenso* the allocation of smokers into average tar level groups.

There are only a few studies that address the question of lower risk from lower tar by investigating *exclusive* users of either low- or high-tar cigarettes (more usually, lifelong filter vs plain tip). In the age groups of high lung cancer incidence, it is not easy to accumulate numbers of smokers of "pure" type, who have never changed from plain to filter tip. Vutuc and Kunze (28) reported a risk reduction of 59% for their middle tar-content category (corresponding roughly to our two middle tar-level groups, combined), compared with their high one (corresponding to our highest tar-level group), with adjustment for age, duration, and intensity of smoking. The authors have included former smokers in their sample without adjusting for cessation: this complicates the issue since if smokers stopped a number of years ago, then they could not have been smoking the lower-tar cigarettes; on the other hand, even short periods of cessation may far outweigh the effect of tar reduction.

The parent data set of which the Vutuc and Kunze sample comprises a subset has been more extensively analyzed by Lubin and co-workers (12). Much of this work addressed filter/nonfilter differences, with attendant definitional difficulties. Restricting themselves to smokers never quitting, they found the equivalent of a 56% reduction in risk for those who smoked only filter cigarettes compared with those who smoked only non-filters, adjusted for duration of smoking; they stated that there was little change after adjustment for age or intensity.

While studies such as the two above offer a sense of methodological purity in their effort to compare undiluted types (lifelong "low-tar," "filter," "high-tar," or "plain"), they are difficult to interpret because populations of lifetime filter-only (low-tar) smokers differ sharply from plain-only (high-tar) smokers. Specifically, among our control smokers (subset B, Table 1), the 11 lifelong filter smokers were significantly different from the 77 lifelong non-filter smokers in the respect that they averaged 10 years younger, started smoking 5 years later, smoked almost a half a pack less per day, and overall had one-third the total packyears exposure. These results are similar to those found in a large series of smoking histories recently assembled by Wynder *et al.* (27). Clearly, behavioral aspects of smoking and age of the smoker need to be controlled carefully, especially in any comparison of users of exclusively one type of cigarette with another type.

The majority of studies on lung cancer risk in relation to tar content have, as in our study, attempted to quantify an hypothesized decreased risk among persons presently smoking low-tar (or filter) cigarettes, after some term of smoking higher tar (or nonfilter) cigarettes. Some of this work suggested a substantial risk reduction. Bross and Gibson (2) examined filter vs non-filter cigarette users as defined by the type currently used. Filter users showed a risk reduction of 44% with adjustment for both duration and intensity of smoking; age was not controlled in the analysis, although the entire study sample of controls was age-matched to the

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cases. Wynder *et al.* (28), who likewise age-matched and adjusted for intensity, found a risk reduction of 41% for their subjects who smoked filters for at least 10 years, relative to plain-tip smokers.

Other studies have suggested a smaller reduction in risk. Wynder and Stellman (30) again compared long-term filter smokers with non-filter users, but adjusted simultaneously for intensity and either age or duration; the reduction for the former group was either 16 or 21%, respectively. Likewise, Hammond *et al.*'s prospective study (8), matching subjects on an extensive variable list, yielded almost identical figures for risk reduction of lung cancer among smokers of low-tar vs high-tar cigarettes, 17% for the 1960–1966 part of the study, 21% for the 1966–1972 part. Lubin *et al.* compared long-term low-tar brand users with long-term high-tar brand users, and found a risk reduction of about 30% (13). This analysis was controlled for number of cigarettes, length of habit, and cessation; the cases and controls being originally age-matched, apparently no adjustment for age was done.

In our study, examination of smoking histories and the distribution of average tar levels convinced us that the defined groups reflect real classes of behavior, especially in 1973–1980: persons in the highest reference group still smoked non-filter cigarettes; the majority, in the two middle groups of the distribution, were smokers of popular and long-established (but changing over time) brands of filter cigarettes; those in the lowest group changed to the lowest-tar cigarettes available.

The initial unadjusted result of Table 2 indicated a risk reduction of half for persons smoking a cigarette in the 14 mg or lower tar range. However, any adjustment for lifetime smoking rendered the apparent risk reduction nonsignificant. Inclusion of other confounders such as age decreased the risk reduction further, to only 17% for the lowest-tar group, a point at which it can hardly even be characterized as nonsignificant but suggestive. As Doll and Peto (3) have concluded, smokers in the age groups that contribute the great bulk of lung cancer cases appear to have been in fact so early and so intensely exposed to tobacco smoke that the only form of tar reduction that gives any significant benefit to them is complete cessation. Kunze and Vutuc (10) arrrived at much the same conclusion.

One simple explanation for our observed absence of significant risk reduction could be that the theoretical benefit of reduction of intake of proven harmful material per cigarette smoked is offset by smoking more cigarettes. Other investigators have surmised variously, for smokers switching to lower-tar cigarettes, that there is no compensatory increase (6, 29), that there might be a small increase (9, 11), that there certainly is an increase (17, 27), or that their data are inappropriate for the question (26); the Surgeon General urges further research (24). Our data indicate that a subgroup of smokers in this study distinctly alters its behavior in such a way as to diminish the putative benefit: cases who smoked cigarettes with the lowest available tar for nearly 20 years also increased the number they smoked by almost half a pack per day. However, at the risk of advancing a *post hoc propter hoc* argument, the fact that controls did not show similar compensation suggests that tar reduction could still be of some benefit.

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In recent years considerable discussion has been devoted to the proposition that, since smokers are not going to quit in large numbers no matter how grim the potential health consequences, perhaps some benefit might be gained by promoting brand-switching, or by redesigning cigarettes (7, 24). The implication of our finding of demonstrated significant compensation is that public health efforts aimed at converting smokers to the use of low-tar cigarettes must simultaneously emphasize the need to avoid smoking more cigarettes. Moreover, should there still be any doubt, efforts to promote smoking cessation and to prevent smoking initiation should be emphasized and intensified however possible.

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Independence of Dysplastic Nevi from Total Nevi in Determining Risk for Nonfamilial Melanoma[1]

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In the determination of risk for melanoma, relatively little is known about the possible independence of two important predictors, total nevi and clinically dysplastic nevi. From a study conducted in Sydney, Australia [see J. J. Nordlund *et al., Cancer Res.* 45, 1855–1861 (1985)], 246 cases of melanoma (excluding 7% of targeted patients with a history of melanoma in a first-degree relative) were compared with 134 nonmelanoma controls. Participants had been examined by a dermatologist and an oncologist. Logistic regression analysis was used and included an age–sex interaction term in computing all estimates of relative risk in this report. Relative risk for melanoma in those with 16+ total nevi was significantly elevated at 1.8 but declined to a statistically nonsignificant level of 1.2 (95% confidence limit (CL): 0.7, 2.0) after adjustment for dysplastic nevi. In contrast, relative risk for melanoma in those with any dysplastic nevi was 7.6 (95% CL: 3.6, 16.0) but was maintained at a similarly elevated and statistically significant level of 7.7 (95% CL: 3.5, 17.1) after adjustment for total nevi. These patterns were even more evident in the younger half of the study population. The analyses suggest that much of the association between TN and nonfamilial melanoma is explained by the presence of dysplastic nevi and, conversely, they imply that dysplastic nevi represent a clinically distinct, qualitative disorder rather than simply a quantitative disorder wherein dysplastic nevi stem merely from an increase in total nevi. The dysplastic nevus syndrome accounts for 32% of all nonfamilial melanomas. © 1988 Academic Press, Inc.

INTRODUCTION

Two lines of research have identified nevocytic markers of risk for cutaneous malignant melanoma. This tumor has been related to a *quantitative* melanocytic change, an increase in numbers of nevi (6, 7, 10, 14). Melanoma is also associated with *qualitative* melanocytic abnormalities, the occurrence of clinically dysplastic nevi (DN) (11, 12, 14), with relative risks for melanoma of sixfold or greater. The latter work stemmed from studies in the familial setting (3, 8), studies which later suggested a 100% lifetime risk (approaching infinite relative risk) in individuals with DN who also belonged to families in which two melanomas had occurred (9).

It is clear that DN are clinically and biologically significant in these rare family kindreds. In the nonfamilial setting, however, the association of DN with melanoma, although substantial, is less strong than in the rare family kindreds reported (3, 8, 9), and for these more common melanomas, some skepticism (1) regarding

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The Effect of Low-Yield Cigarette Smoking on Lung Cancer Risk

ERNST L. WYNDER, MD, AND GEOFFREY C. KABAT, PhD

The effect of low-yield (filter) cigarette (LYC) smoking on lung cancer risk, by two broad histologic groupings (Kreyberg I [KI] and II [KII]), was examined in a large case–control study. Among males, there were 1278 KI patients and 2408 patient controls matched on age, race, hospital, and year of interview and 807 KII patients and 1543 matched patient controls. Among females, there were 513 KI patients and 960 matched patient controls and 499 KII patients and 932 matched patient controls. For the purposes of estimating the reduction in risk due to smoking filter rather than nonfilter cigarettes, odds ratios (OR) for smokers of filter cigarettes only, short-term switchers (*i.e.*, switchers from nonfilter to filter cigarettes who had smoked the latter for 1 to 9 years), and long-term switchers (*i.e.*, switchers to filter cigarettes who had smoked filter cigarettes for 10+ years) were calculated relative to smokers of nonfilter cigarettes only (OR = 1.00). Logistic regression was used to obtain estimates adjusted for cigarettes per day (CPD), inhalation, age, and years of schooling. Filter-only smokers of both sexes appeared to have a reduced risk of KI lung cancer (OR = 0.69, 95% confidence interval [CI], 0.37 to 1.27 in males; OR = 0.64, 0.30 to 1.35 in females). Male long-term switchers had a significantly reduced risk (OR = 0.66, 0.49 to 0.90), and female long-term switchers had a nonsignificant reduced risk of KI lung cancer (OR = 0.74, 0.40 to 1.36). The risks of short-term switchers were closer to 1.00 (OR = 0.83, 0.59 to 1.17 in males; OR = 0.99, 0.49 to 2.03 in females). Evidence of a reduction in risk of KII was weaker in males and undetectable in females.

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BECAUSE THE SMOKING of tobacco, and especially of cigarettes, is the principal cause of lung cancer, the important question is how the tobacco–cancer link can be broken. Ideally, people would be convinced never to start smoking. Next in line in desirability would be to get smokers to quit the habit. However, because many people have been unable or unwilling to stop smoking, the last available alternative would be to lower the tar yield of cigarettes to such an extent that these products may be rendered less harmful. This report presents data from an ongoing study designed to assess the effects of the use of low-yield cigarettes (LYC) on lung cancer risk. With the prolonged use of LYC and the finding that a proportion of smokers now reaching the cancer age has smoked such cigarettes exclusively, a more accurate assessment of their effects should be possible.

Materials and Methods

The database used in this analysis is part of a large ongoing study of tobacco related diseases, which has been described previously.[1,2] One thousand seventy-eight male and 513 female Kreyberg I (KI) lung cancer patients (including squamous cell, large cell, and oat cell lung cancers) and 807 male and 499 female Kreyberg II (KII) lung cancer patients (including adenocarcinoma, bronchiolar, and alveolar cell carcinoma) were interviewed between 1977 and 1984.

Two patient controls were randomly sought for each

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TABLE 1. Distribution of Socio-Demographic Factors in Male Kreyberg I and II Lung Cancer Patients and Patient Controls

	KI		KII	
	Patients	Patient controls	Patients	Patient controls
No.	1278	2408	807	1543
Age at interview (yr)				
<45	6%	6%	10%	12%
45–54	19%	20%	24%	23%
55–64	43%	42%	38%	38%
65–74	29%	29%	25%	25%
75+	3%	3%	4%	3%
Education (yr)				
1–8	24%	15%	16%	12%
9–12	46%	42%	42%	38%
13–15	12%	15%	15%	15%
16	11%	14%	13%	14%
17+	7%	14%	14%	20%
Religion				
Protestant	35%	37%	26%	27%
Catholic	48%	37%	50%	40%
Jewish	9%	20%	18%	25%
Other	2%	3%	2%	3%
None	6%	4%	4%	5%
Occupation				
Prof/manager	28%	39%	37%	45%
Skilled	38%	36%	36%	32%
Semi-skilled	19%	14%	15%	14%
Unskilled	15%	11%	11%	8%

KI: Kreyberg I; KII: Kreyberg II.

patient from the large pool of patients with nontobacco-related diseases requiring hospitalization interviewed throughout the study period. These patient controls were matched to lung cancer patients on the basis of age (±5 years), sex, race, hospital, and year of interview. Two thousand four hundred eight male patient controls and 959 female patient controls were selected for KI lung cancer patients. For KII lung cancer patients, 1543 male patient controls and 932 female patient controls were selected.

Study subjects were interviewed in the hospital by trained interviewers using a structured questionnaire that contained questions on demographic factors, smoking history, medical history, and other potential risk factors or confounders (*i.e.*, alcohol consumption and self-reported chemical exposure). Detailed smoking histories were obtained including brand of cigarette, length of cigarette, number of cigarettes smoked per day (CPD), and duration of smoking each brand, for up to four brands per person. The cumulative number of years that all brands were smoked was recorded for the total smoking duration. The average number of CPD of each brand consumed in the last 10 years before the interview was calculated.

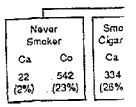
The analysis was restricted to current cigarette only smokers who had smoked for at least 10 years before being interviewed. For males and females with both types of lung cancer, 13 patients and 30 patient controls had smoked for less than 10 years. Long-term cigarette-only smokers (those who had smoked for at least 10 years) were further divided into the following four groups according to their lifetime smoking habits: nonfilter only, switchers from nonfilter to filter who had smoked filter cigarettes for 1 to 9 years, switchers who had smoked filter cigarettes for 10+ years, and filter-only smokers.

Point estimates of the relative risk with test-based 95% confidence intervals (CI) were calculated using Miettinen's method.[3] Potential confounding factors were taken into account by stratification, and adjusted relative risks were computed using the Mantel–Haenszel summary estimated odds ratio (OR).[4] Logistic regression was used to obtain estimates of the effect of "filter only" and of switching to filter *versus* "nonfilter only" adjusted for other important variables such as CPD, inhalation, age, and years of education. CPD was categorized as follows: 1 to 10 (referent category), 11 to 20, 21 to 30, 31 to 40, and 41+. Inhalation was categorized into "inhale deeply" *versus* all other responses ("inhale moderately," "slightly," and "not at all"). Age and years of education were entered as continuous variables.

TABLE 2. Distribution of Socio-Demographic Factors in Female Kreyberg I and II Lung Cancer Patients and Patient Controls

	KI		KII	
	Patients	Patient controls	Patients	Patient controls
No.	513	960	499	932
Age at interview (yr)				
<45	8%	7%	14%	12%
45–54	22%	22%	25%	26%
55–64	42%	41%	33%	35%
65–74	25%	26%	24%	25%
75+	3%	3%	4%	2%
Education (yr)				
1–8	14%	11%	10%	11%
9–12	56%	53%	54%	50%
13–15	18%	19%	20%	20%
16	7%	10%	10%	9%
17+	5%	7%	5%	10%
Religion				
Protestant	34%	33%	26%	26%
Catholic	47%	41%	41%	45%
Jewish	14%	19%	27%	24%
Other	2%	3%	2%	2%
None	4%	3%	3%	2%
Occupation				
Prof/manager	16%	20%	16%	21%
Skilled	36%	35%	37%	35%
Semi-skilled	7%	7%	7%	6%
Unskilled	8%	6%	6%	6%
Housewife/misc.	34%	32%	34%	31%

KI: Kreyberg I; KII: Kreyberg II.



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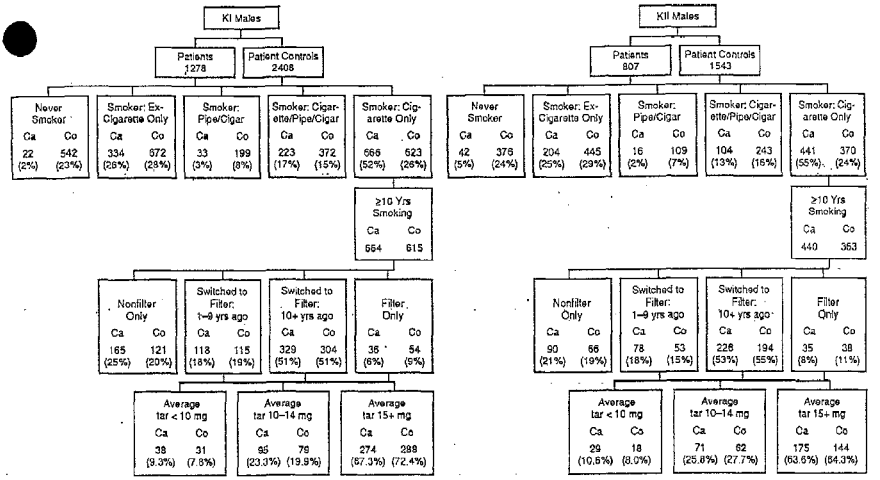
KI Males
Patients 1278
Patient Controls 2408
Never Smoker Ca 22 (2%) Co 542 (23%)
Smoker: Ex-Cigarette Only Ca 334 (26%) Co 672 (28%)
Smoker: Pipe/Cigar Ca 33 (3%) Co 199 (8%)
Smoker: Cigarette/Pipe/Cigar Ca 223 (17%) Co 372 (15%)
Smoker: Cigarette Only Ca 666 (52%) Co 623 (26%)
≥10 Yrs Smoking Ca 564 Co 615
Nonfilter Only Ca 165 (25%) Co 121 (20%)
Switched to Filter: 1–9 yrs ago Ca 118 (18%) Co 115 (19%)
Switched to Filter: 10+ yrs ago Ca 329 (51%) Co 304 (51%)
Filter Only Ca 35 (6%) Co 54 (9%)
Average tar < 10 mg Ca 38 (9.3%) Co 31 (7.8%)
Average tar 10–14 mg Ca 95 (23.3%) Co 79 (19.9%)
Average tar 15+ mg Ca 274 (67.3%) Co 288 (72.4%)
KII Males
Patients 807
Patient Controls 1543
Never Smoker Ca 42 (5%) Co 376 (24%)
Smoker: Ex-Cigarette Only Ca 204 (25%) Co 445 (29%)
Smoker: Pipe/Cigar Ca 16 (2%) Co 109 (7%)
Smoker: Cigarette/Pipe/Cigar Ca 104 (13%) Co 243 (16%)
Smoker: Cigarette Only Ca 441 (55%) Co 370 (24%)
≥10 Yrs Smoking Ca 440 Co 363
Nonfilter Only Ca 90 (21%) Co 66 (19%)
Switched to Filter: 1–9 yrs ago Ca 78 (18%) Co 53 (15%)
Switched to Filter: 10+ yrs ago Ca 226 (53%) Co 194 (55%)
Filter Only Ca 35 (8%) Co 38 (11%)
Average tar < 10 mg Ca 29 (10.6%) Co 18 (8.0%)
Average tar 10–14 mg Ca 71 (25.8%) Co 62 (27.7%)
Average tar 15+ mg Ca 175 (63.6%) Co 144 (64.3%)

FIG. 1. Kreyberg I and II male lung cancer patients and their age and hospital-matched patient controls by smoking history.

Results

Tables 1 and 2 present the distribution of demographic variables for KI and KII lung cancer patients and their respective patient controls. KI male patients were older than those with KII (25% *versus* 34% <55 years of age), had fewer years of education (70% *versus* 58% with <12 years of schooling), had lower occupational status (34% *versus* 26% had semiskilled or unskilled jobs), and included fewer Jews (9% *versus* 18%). Similar although less marked differences were seen for female patients with KI and KII (age [30% *versus* 39% <55 years of age], education [70% *versus* 64% with <12 years of schooling], and religion [14% *versus* 27% Jews]).

Figures 1 and 2 present data on the smoking habits of patients and patient controls. The purpose of presenting the data in this manner is to show differences between patients and patient controls, men and women, and KI and KII type lung cancer patients according to percentage of nonsmokers, exsmokers, cigar/pipe only smokers, mixed smokers, and cigarette-only smokers by type of cigarette and duration of smoking.

As has been frequently reported, few never-smokers were found among KI male patients (2%) whereas 23% of the patient controls were never-smokers. The percentage of exsmokers was about the same in patients and patient controls (26% *versus* 28%), pipe and cigar smokers comprised 3% *versus* 8%, and there was a similar percentage of mixed smokers. The remaining 52% of the patients and 26% of the patient controls were current smokers who have smoked cigarettes only throughout their life ("present cigarettes-only" smokers). Virtually all present cigarettes-only smokers had smoked filter cigarettes for more than 10 years (the estimated minimum time interval necessary to detect an impact of smoking LYC on lung cancer risk). Most persons in the cancer age began their smoking habit with high-yield, nonfilter cigarettes. Thus, only 36 male KI patients and 54 patient controls reported having smoked filter cigarettes exclusively. For analysis of the question whether long-term smoking of filter cigarettes (>10 years) reduces the relative risk of KI lung cancer, only 365 patients and 358 patient controls (switchers of 10+ years and filter-only smokers) were available out of 1278 patients and 2408 patient controls.

Among male KII patients, there was a larger percentage of never-smokers (5%) than among men with KI (2%). There were more men with KI (1278) compared with those with KII lung cancer (807), giving a KI:KII ratio of 1.6. Thirty-five (8%) of the KII patients and 38 (11%) of their patient controls had smoked filter cigarettes exclusively, whereas 226 (53%) of the patients and 194 (55%) of their patient controls had switched to filter cigarettes and had smoked them for more than 10 years.

Figure 2 shows that among women, there were more nonsmokers among KII than KI patients, (19% *versus* 6%). Also, there was a larger percentage of never-smokers among female patient controls for KII (52%)

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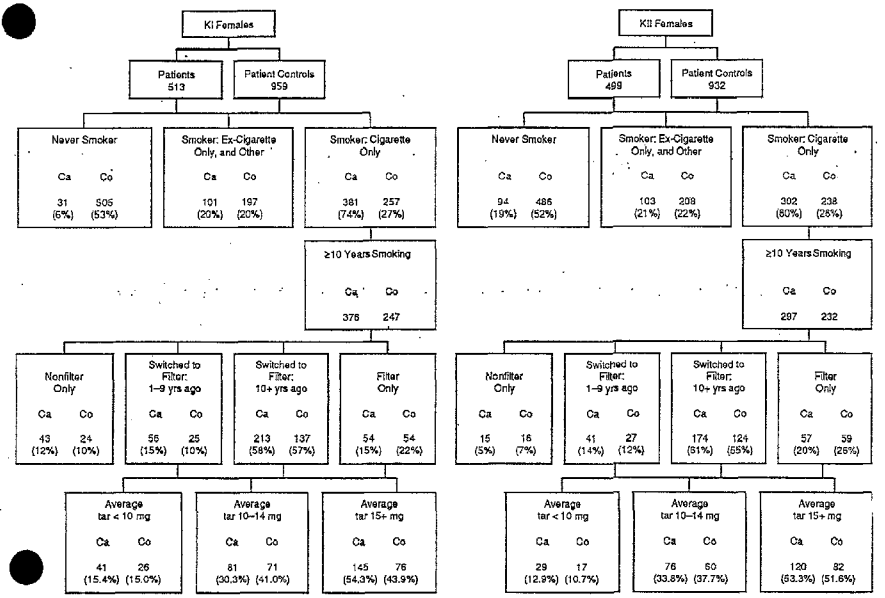

FIG. 2. Kreyberg I and II female lung cancer patients and their age and hospital-matched patient controls by smoking history.

compared with the male patient controls for KII (24%). The number of switchers of 10+ years among KI patients was 213 (58%) *versus* 137 (57%) in the patient controls, whereas among KII patients, it was 174 (61%) *versus* 124 (55%) in the patient controls. Relatively more women than men smoked filter cigarettes exclusively (15% of KI patients and 22% of patient controls; 20% of KII patients and 26% of patient controls).

Tables 3 and 4 show crude OR for KI and KII lung cancer by amount smoked and by sex. This table includes never-smokers and current smokers of cigarettes only who have smoked for 10 or more years. Both histologic groupings show an increase in the OR with increasing number of cigarettes smoked. The OR for KI are larger than those for KII at each CPD level due to the smaller proportion of never-smokers among KI compared with KII patients.

Tables 5 and 6 present the OR for KI and KII lung cancer of smokers of filter cigarettes only and of "short-term switchers" (1 to 9 years) and "long-term switchers"

TABLE 3. Odds Ratios for Kreyberg I and II Lung Cancer by Amount Smoked*

	Males							
	KI				KII			
	Patients	Patient controls	OR	CI	Patients	Patient controls	OR	CI
Never smoked	22	542	1.00	—	42	376	1.00	—
1–10 CPD	50	93	13.25	8.35–21.02	15	55	2.44	1.29–4.62
11–20 CPD	153	238	15.84	10.71–23.43	126	134	8.42	5.81–12.20
21–30 CPD	120	100	29.56	19.79–44.17	98	57	15.39	10.24–23.14
31–40 CPD	162	106	37.65	25.56–55.47	99	80	11.08	7.46–16.45
41+ CPD	169	65	64.05	43.10–95.19	95	30	28.35	18.25–44.04
Total	676	1144			475	732		

KI: Kreyberg I; KII: Kreyberg II; OR: odds ratio; CI: 95% confidence interval; CPD: cigarettes per day.

* Includes current smokers of cigarettes only who have smoked for 10 years or more.

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TABLE 4. Odds Ratios for Kreyberg I and II Lung Cancer by Amount Smoked*

	Females							
	KI				KII			
	Patients	Patient controls	OR	CI	Patients	Patient controls	OR	CI
Never smoked	31	505	1.00	—	94	486	1.00	—
1–10 CPD	27	67	6.56	3.90–11.04	26	44	3.06	1.83–5.11
11–20 CPD	126	113	18.16	12.44–26.53	100	115	4.50	3.22–6.28
21–30 CPD	57	35	26.53	16.94–41.54	60	33	9.40	6.13–14.41
31–40 CPD	111	19	95.17	60.71–149.18	72	27	13.79	9.01–21.10
41+ CPD	49	9	88.69	52.33–150.31	32	8	20.68	11.21–38.17
Total	401	748			384	713		

KI: Kreyberg I; KII: Kreyberg II; OR: odds ratio; CI: 95% confidence interval; CPD: cigarettes per day.

* Includes current smokers of cigarettes only who have smoked for 10 years or more.

TABLE 5. Adjusted* Odds Ratios and 95% Confidence Intervals for Filter-Only Smokers and Short-Term and Long-Term Switchers Compared With Nonfilter-Only Smokers

	Males							
	KI				KII			
	Patients	Patient controls	OR	CI	Patients	Patient controls	OR	CI
Nonfilter only	165	121	1.00	—	90	66	1.00	—
Switchers (1–9 yr)	120	122	0.83	0.59–1.17	83	59	0.96	0.61–1.51
Switchers (10+ yr)	330	304	0.66	0.49–0.90	226	195	0.79	0.53–1.18
Filter only	36	54	0.69	0.37–1.27	35	38	0.87	0.43–1.54

KI: Kreyberg I; KII: Kreyberg II; OR: odds ratio; CI: 95% confidence interval.

* Adjusted for cigarettes per day, age, inhalation, and years of education in logistic regression models.

(10+ years) relative to smokers of nonfilter cigarettes only. Estimates were obtained from separate logistic regression models for filter only, short-term switcher, and long-term switcher *versus* nonfilter only, which included CPD, inhalation, age, and years of education. Male "filter-only" smokers had an adjusted OR of 0.69 (95% CI 0.37 to 1.27) for KI lung cancer, short-term switchers had an OR of 0.83 (0.59 to 1.17), and long-term switchers had an OR of 0.66 (0.49 to 0.90) compared with smokers of nonfilter cigarettes only. The corresponding OR for KII were 0.87 (0.43 to 1.54), 0.96 (0.61 to 1.51), and 0.79 (0.53 to 1.18), respectively. In females, the OR for KI lung cancer was 0.64 (0.30 to 1.35) for filter-only smokers, 0.99 (0.49 to 2.03) for short-term switchers, and 0.74 (0.40 to 1.36) for long-term switchers. Because of the small numbers of nonfilter-only smokers among KII patients and patient controls, short-term switchers (1 to 9 years) were combined with

TABLE 6. Adjusted* Odds Ratios and 95% Confidence Intervals for Filter-Only Smokers and Short-Term and Long-Term Switchers Compared With Nonfilter-Only Smokers

	Females								
	KI					KII			
	Patients	Patient controls	OR	CI		Patients	Patient controls	OR	CI
Nonfilter only	43	24	1.00	—	NF and STS	66	48	1.00	—
Switchers (1–9 yr)	62	27	0.99	0.49–2.03	LTS	174	124	0.99	0.76–1.29
Switchers (10+ yr)	215	137	0.74	0.40–1.36					
Filter only	54	54	0.64	0.30–1.35	Filter only	57	59	0.96	0.62–1.47

KI: Kreyberg I; KII: Kreyberg II; OR: odds ratio; CI: 95% confidence interval; NF: nonfilter; STS: short-term switchers.

* Adjusted for cigarettes per day, age, inhalation, and years of education in logistic regression models.

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TABLE 7. Summary of Epidemiologic Studies of Effect of Type of Cigarette Smoked (Filter/Nonfilter) on Lung Cancer Risk

Study	Type	Population	Findings
Gross & Gibson[15] (1968)	Case–control	974 white male cases and 974 white male controls admitted to Roswell Park between 1960 and 1966	OR for lung cancer for current filter and nonfilter smokers relative to nonsmokers by duration and quantity smoked: filter, 3.8; nonfilter, 6.5
Wynder *et al.*[11] (1970)	Case–control	210 male and 30 female KI lung cancer cases and twice the number of controls	Odds of lung cancer for long-term nonfilter smokers *versus* long-term filter smokers (adjusted for CPD):1.8 (1.1 to 3.0)
Hammond *et al.*[16] (1976)	Prospective	Over a million subjects enrolled in the American Cancer Society study between 1959 and 1960	Age-standardized mortality ratios of lung cancer in two time periods, by tar content of cigarettes usually smoked, by sex:

		Mortality ratio		
		Tar content (mg/cig)		
Sex	Period	25.8–35.7	17.6–25.7	<17.6
M	1960–1966	1.0	0.96	0.83
M	1966–1972	1.0	0.94	0.79
F	1960–1966	1.0	0.84	0.57
F	1966–1972	1.0	0.73	0.62

Dean *et al.*[17] (1977)	Case–control	616 men and 150 women who died of lung cancer between 1966 and 1972; relatives of patients were interviewed; 1563 male and 2958 female controls were selected randomly from electoral registries	OR for filter compared with nonfilter smokers (age, 35+ years) standardized by age and quantity of CPD: males, 0.54 (0.40 to 0.73); females, 0.68 (0.42 to 1.11)
Hawthorne & Fry[18] (1978)	Prospective	18,786 subjects who completed a multi-phase screening exam	Relative mortality (based on 80 deaths) in current male cigarette smokers (standardized for age and CPD) demonstrated no substantial risk difference for filter *versus* plain cigarettes:

Type of Cigarettes	Lung cancer
Filter	89
Plain	107

Wynder & Stellman[2] (1979)	Case–control	557 male and 127 female cases with KI lung cancer and 4835 male and 4712 female controls	Nonfilter smokers (current smokers of nonfilter cigarettes) had elevated OR relative to long-term filter smokers (current smokers who used filter cigarettes currently and at least 10 years), but the differences did not reach statistical significance: males, OR = 1.26 (0.97 to 1.64); females, OR = 1.37 (0.72 to 2.60)
Kunze & Vutuc[19] (1980)	Case–control	1600 male lung cancer cases and 3200 controls collected from 15 clinical departments of hospitals between 1976 and 1979	Lifetime tar exposure was estimated by a score including duration (yr), CPD, and tar level; the following OR were calculated for the KI group:

Lifetime tar exposure	OR*	*P*-value
<500	2.0	Not significant
501–1000	2.6	<0.01
1001–2000	5.3	<0.01
2001–3000	7.2	<0.01
3001–4000	7.7	<0.01
4001–5000	9.5	<0.01
>5000	7.8	<0.01

* Relative to nonsmokers

Rimington[20] (1981)	Prospective	10,414 male volunteers for mass radiography were observed	Age-standardized incidence of lung cancer per 1000 among 5438 male cigarette smokers was calculated:

	Age-standardized incidence rates	
Quantity of CPD	Filter smoker (n = 239)	Nonfilter smoker (n = 304)
1–9	5.8	13.3
10–19	17.5	25.9
20+	26.9	44.6
Total	19.7	30.4

Study

Vutuc & Kunze[22] (1982)

Vutuc & Kunze[21] (1983)

Lubin *et al.*[23] (1984)

Benhamou *et al.*[24] (1985)

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TABLE 7. (*Continued*)

Study	Type	Population	Findings
Vutuc & Kunze[22] (1982)	Case–control	200 female lung cancer cases (of whom 130 were KI) and 400 controls	Lifetime tar exposure was estimated by means of a score including duration (yr), number of CPD, and tar level; the following OR were calculated for KI for different lifetime tar exposure groups relative to nonsmokers: Lifetime tar exposure / OR / *P*-value <500 / 1.45 / <0.01 501–1000 / 4.21 / <0.01 1001–2000 / 4.79 / <0.01 2001–3000 / 4.91 / <0.01 >3000 / 6.75 / <0.01
Vutuc & Kunze[21] (1983)	Case–control	1580 male lung cancer cases and 3160 controls interviewed in 15 hospitals between 1976 and 1980; after excluding subjects for occupational risk factors, 252 cases (16%) and 839 controls (27%) were used in the analysis	Tar level / OR*,† / 95% CI Group 1 / 10.9 / (3.9–30.7) Group 2 / 20.6 / (12.3–34.8) Group 3 / 36.7 / (27.0–49.9) * Relative to nonsmokers (OR = 1.0) † Adjusted for duration, quantity, and age
Lubin *et al.*[23] (1984)	Case–control	7804 lung cancer cases and 15,207 hospital-based controls from seven locations in Western Europe	OR* for lung cancer by proportion of years nonfilter brands were used, adjusted for years of cigarette use and CPD. Proportion of yr of nonfilter brands smoked / Males / Females 0.01–0.49 / 1.5 / 1.8 0.50–0.69 / 1.4 / 1.7 0.70–0.83 / 1.7 / 1.9 0.84–0.99 / 1.7 / 2.1 1.00 (all nonfilter) / 1.7 / 2.0 * Relative to lifelong filter smokers (OR = 1.0)
Benhamou *et al.*[24] (1985)	Case–control	1217 male lung cancer cases and 1915 controls	Smokers of nonfilter cigarettes had significantly higher OR for KI lung cancer compared with smokers of filter cigarettes (OR = 18.1 and 10.9, respectively); when covariates were taken into account, the OR for lifetime nonfilter smokers relative to lifetime filter smokers was 1.23

KI: Kreyberg I; OR: odds ratio; CPD: cigarettes per day; CI: confidence interval.

nonfilter smokers as the reference category. The OR for filter-only smokers was 0.96 (0.62 to 1.47) and 0.99 (0.76 to 1.29) for long-term switchers.

Discussion

As we reported 36 years ago,[5] smoking, especially in the form of cigarettes, is the principal cause of lung cancer. Much has changed since that time in respect to public awareness of the health hazards of smoking. Compared with 1950, relatively fewer men, although more women, are smoking. The greater percentage of men who have never smoked or who are confirmed long-term exsmokers has no doubt contributed to the declining incidence rate of lung cancer observed among younger males in the United Kingdom and the US.[6,7] Most marked, as to be expected, is a reduction of lung cancer in groups such as physicians, a large proportion of whom have given up smoking.[8,9] Clearly, never having smoked or having ceased smoking early in life are the best means of reducing tobacco-related diseases.

The reduction in male lung cancer incidence has been experienced despite the fact that whereas we have relatively fewer smokers, those who continue to smoke consume more cigarettes than smokers of two decades ago. At that time, 19% of our male hospital patient control population smoked in excess of 20 CPD,[5] compared with more than 52% among current male smokers today.[10]

On the basis of studies we reported in 1970 and 1979,[2,11] we anticipated a reduction of lung cancer incidence, especially among younger cohorts who had

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smoked filter cigarettes for at least 10 years and among the smaller proportion of subjects who had smoked filter cigarettes exclusively.

The hypothesis is that the lower tar yields of cigarettes reduce exposure to carcinogens and promoters in tobacco smoke and, thus, reduce the risk of lung cancer for the smoker. However, smokers of LYC are known to compensate for nicotine uptake from the smoke by more frequent puff-drawing, deeper and more intense inhalation, and an increased number of CPD.[12–14] Thus, a cigarette yielding 10 mg of tar should pose a lower risk than one with a 20-mg tar delivery, provided that smokers do not fully compensate for the differences. How well did our findings support this hypothesis?

Our data suggest that smokers of filter cigarettes experience some reduction in lung cancer risk relative to smokers of nonfilter cigarettes. The OR for KI lung cancer for filter-only smokers relative to nonfilter-only smokers was 0.69 (0.37 to 1.27) in males and 0.64 (0.30 to 1.35) in females. Male long-term switchers had a significantly reduced OR for KI lung cancer (0.66, 0.49 to 0.90). For female long-term switchers, the OR for KI lung cancer was 0.74 (0.40 to 1.36). There was also a suggestion of a slight reduction in risk for KII lung cancer among male lifetime filter smokers and long-term switchers. However, there was no evidence of a reduction in risk for KII lung cancer in female filter-only smokers and long-term switchers.

Although these data were adjusted for number of CPD, it is possible that patients who switched to filter cigarettes increased their CPD to a greater extent than patient controls who switched, and that lung cancer patients may have underreported their CPD. However, if patients did in fact underreport their CPD to a greater extent than the patient controls, the real impact of the LYC would be even greater.

The data presented here are consistent with previous reports by us and others[15–24] that reduction of tar exposure leads to a reduction of lung cancer risk (Table 7). The magnitude of the reduction in risk for KI lung cancer for long-term filter smokers appears to be on the order of 25% to 35% in this study. These results are in the same range as those of previous studies.

The overall tar yields of cigarettes, including nonfilter cigarettes, have declined since the early 1950s. The sales-weighted average tar yield of nonfilter cigarettes declined from 37 mg in 1954 to approximately 20 mg in 1983, whereas the average tar yield of filter cigarettes dropped from 27 to 12 mg.[25] During the same period, the average nicotine level of cigarettes dropped from 2.3 to 1.0 mg. The largest reduction in lung cancer risk among current smokers should, therefore, be seen in those who have smoked filter cigarettes and especially low-yield filter cigarettes throughout their lives. As can be seen in Figures 1 and 2, we currently have insufficient numbers in this latter group for analysis. A study of the effect of low-yield filter cigarettes (<10 mg) and medium-yield filter cigarettes (10 to 14 mg) compared with high-tar filter cigarettes (15+ mg) will be reported subsequently.

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GARFINKEL, L.

"SMOKING AND LUNG CANCER IN WOMEN (FINDINGS IN A PROSPECTIVE STUDY)"

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LE 1—*continued*

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TAR CONTENT OF CIGARETTES IN RELATION TO LUNG CANCER

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Kaufman, D. W. (Slone Epidemiology Unit, Boston U. School of Medicine, Brookline, MA 02146), J. R. Palmer, L. Rosenberg, P. Stolley, E. Warshauer, and S. Shapiro. *Tar content of cigarettes in relation to lung cancer. Am J Epidemiol* 1989;129:703–11.

Although it is generally considered established that the risk of lung cancer is directly related to the tar content of cigarettes, an examination of the results of previous studies does not yield conclusive evidence in favor of the hypothesis. The authors evaluated this issue in a study of 881 cases of lung cancer and 2,570 hospital controls who were 40 to 69 years of age; data were collected by interview in hospitals in the United States and Canada from November 1981 to June 1986. For each year of smoking, cigarette brands were classified according to their tar content as published in regular Federal Trade Commission reports (from 1967 to 1985) or the *Reader's Digest* (from 1957 to 1966). Tar values for years for which there was no published information were estimated by interpolation. Smokers were divided, according to the tar content of their cigarette brands averaged over a specified period, into low (<22 mg/cigarette), medium (22–28 mg/cigarette), and high (≥29 mg/cigarette) tar smokers. When the average tar content was based on cigarettes smoked at least 10 years previously, the relative risk estimates for medium and high tar smokers compared with low tar smokers were 3.0 and 4.0 after control for potentially confounding factors, including the number of cigarettes smoked per day. The trend was significant ($p = 0.002$). The tendency for the risk of lung cancer to increase with increasing tar content was consistent among men and women. The results provide further support for the hypothesis that the tar content of cigarettes is directly related to lung cancer risk. However, the data were limited in that there were very few subjects whose lifetime tar exposure averaged less than 10 mg/cigarette.

lung neoplasms; smoking; tars

It is generally accepted that the risk of lung cancer is related to the tar content of cigarettes, with smokers of low tar cigaretts [redacted] a higher risk than non-

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smokers but a lower risk than smokers of high tar cigarettes. This has considerable biologic plausibility, because "tar" contains known carcinogens, including benzo(*a*)pyrene, dibenz(*ah*)anthracene, 5-methylchrysene, and other polyaromatic hydrocarbons (1). Four epidemiologic studies have been published with data on tar content (2–5). In two, the results suggested that tar is related to lung cancer risk. The American Cancer Society conducted a large-scale follow-up study in which over 1,000 cases of lung cancer developed during six years of follow-up (2). Among men, the standardized mortality ratio for smokers of low tar cigarettes compared with smokers of high tar cigarettes was 0.8; compared with smokers of medium tar cigarettes, it was 0.9. These results were not statistically significant. Among women, the corresponding standardized mortality ratios were 0.6 and 0.7, respectively, and they were statistically significant. In a case-control study of women from Austria, the relative risk estimates for low, medium, and high tar smokers relative to nonsmokers were 2.6, 4.4, and 8.9, respectively (3). These estimates were based on 188 cases who were smokers, and the trend was statistically significant.

The results of the other two studies were equivocal. In the Whitehall study, after 10 years of follow-up there were 108 fatal cases of lung cancer among smokers who inhaled (4). For those who smoked less than 20 cigarettes per day, there was a nonsignificant increase in the mortality with increasing tar content; among the heaviest smokers (51 cases) there was no increase at all. Among noninhalers, lung cancer mortality did rise significantly with increasing tar, but this observation was based on only 35 cases. In a four-year follow-up study using data from Kaiser Permanente (5), there was no association between tar content and lung cancer risk; again, this was based on small numbers (a total of 35 cases of lung cancer).

Two additional studies contained information on filter and nonfilter cigarettes (an indirect measure of low and high tar cigarettes). In the Manchester Filter Study, smokers were followed for up to seven years, and there were 104 cases of lung cancer (6). The incidence was approximately 50 per cent higher among smokers of nonfilter cigarettes than among smokers of filter cigarettes, and the pattern was consistent within strata of age and number of cigarettes smoked per day. In a case-control study conducted by Wynder and Stellman with approximately 700 cases of lung cancer, the relative risk estimate was consistently higher for nonfilter smokers, regardless of how much they smoked (7).

To summarize the evidence, most of the published findings support the hypothesis that the tar content of cigarettes is related to the risk of lung cancer, but the results are not compelling: Some were not statistically significant, some were based on indirect measures of the tar content, and some provided no evidence of association.

Since 1976, we have been collecting data on numerous factors from patients with serious illnesses, including lung cancer, in a multipurpose case-control surveillance system (8). This data base has provided the opportunity to further evaluate the tar hypothesis.

Materials and Methods

In case-control surveillance, specially trained nurses stationed in hospitals administer a standard interview to patients

provided the patients, to the nurse-interviewers who collected the data, to Leonard Gaetano for assistance with data management, and to Cynthia Whear for word processing.

The following hospitals participated in the study: *Boston*: Beth Israel Hospital, Newton-Wellesley Hospital, Mt. Auburn Hospital, Massachusetts General Hospital; *New York*: Memorial Sloan-Kettering Cancer Center, New York Hospital, Lenox Hill Hospital; *Philadelphia*: Hospital of the University of Pennsylvania, Hahnemann University Hospital, Lankenau Hospital, Medical College of Pennsylvania Hospital, Montgomery Hospital, Pennsylvania Hospital, Presbyterian Hospital, Thomas Jefferson University Hospital; *Baltimore*: The Johns Hopkins Hospital; *Tucson*: University of Arizona Medical Center; *London, Ontario, Canada*: St. Joseph's Hospital.

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with a wide variety of illnesses. These include diseases of particular interest (e.g., various cancers) and conditions generally suitable as control diagnoses. The information obtained includes personal characteristics (e.g., age), habits (e.g., tobacco and alcohol use), relevant medical history, and a lifetime history of medication use. After the patients are discharged from hospital, details of their conditions, including the primary reasons for admission, are abstracted from the hospital records. This system provides a data base which can be used to evaluate hypotheses of interest. Cases of a particular disease and controls with other conditions are selected, and standard case-control analyses are conducted.

The data reported here were collected from November 1981 to June 1986 in hospitals in Boston, New York, Philadelphia, Baltimore, Tucson, and London, Ontario, Canada. The refusal rate of patients approached for interview was 4 per cent.

Cases

All interviewed men and women aged 40

TABLE 1

Selected characteristics of lung cancer cases and hospital controls aged 40–69 years, US and Canada hospitals, November 1981–June 1986

	Cases (n = 881)		Controls (n = 2,570)	
	No.	%	No.	%
Sex				
Male	534	61	998	39
Female	347	39	1,572	61
Age (years)				
40–49	119	14	977	38
50–59	363	41	852	33
60–69	399	45	741	29
Race				
White	721	82	2,041	79
Nonwhite	160	18	529	21
Years of education				
<12	243	28	503	20
12–15	479	54	1,338	52
≥16	147	17	714	28
Unknown	12	1	15	1
City of hospital admission				
Boston	56	6	659	26
New York	297	34	606	24
Philadelphia	465	53	993	39
Baltimore	60	7	288	11
Tucson	2	0	17	1
London, Ontario, Canada	1	0	7	0

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1985 (there were no reports available for the years 1969, 1971, 1972, 1979, 1980, and 1982) (9–18) and by the *Reader's Digest* (based on similar laboratory methods) for the years 1957, 1958, 1959, 1961, 1963, and 1966 (19–24) to determine an individual's tar exposure. Cigar and pipe smoking were not considered.

It was first necessary to estimate values for the years for which no report was available; this was done by linear interpolation for the missing years after 1959. For the years before 1957, that is, before any reports were available, we made the assumption that the tar values were the same as the earliest reported value for each cigarette. (If anything, they were likely to have been higher, but there was no way to document this.)

For each individual, we assigned a tar value for each year of smoking. For some, the process was straightforward, because they only smoked one brand of cigarettes, or at most, two; that is, the sum of the durations of smoking the two reported brands equalled the total duration of smoking. When the sum of durations was less then the total duration, we assumed that the brand smoked the longest was smoked in the middle of the period before the most recent brand was smoked. Tar values for the years between the assumed end of smoking the longest-smoked brand and the beginning of smoking the most recent brand were then estimated by linear interpolation. Values for the period before beginning smoking of the longest-smoked brand were estimated to be equal to the reported tar values for that brand. (This last approach was also used when there was only information on a single brand and the duration of smoking that brand did not equal the total duration.) Implicit in this process was the further assumption that when subjects switched brands, it was to a cigarette with similar or lower tar, and not to a higher tar brand. This assumption was reasonable on the basis of our data: Over 80 per cent of the smokers who switched did so to a similar or lower tar brand.

We then calculated average tar values (in milligrams per cigarette) for each individual (using a simple yearly average). In addition to overall averages, average values were calculated for cigarettes smoked in specific periods (e.g., at least 10 years before admission), because of the possibility that smoking during those periods was most relevant in the etiology of lung cancer. The average values were the primary measure of tar content used in this study.

Data analysis

Relative risks were estimated for various categories of cigarette smoking according to number smoked per day and tar level. The reference category for some estimates was never smokers. Most of the comparisons were confined to smokers, however, and in these instances the reference category was those in the lowest category of tar values. Ex-smokers were not included in the analyses of tar level because the risk of lung cancer declines with an increasing interval since quitting, and taking this into account would have needlessly complicated the presentation of results. To minimize misclassification from incomplete brand histories, the analyses of tar level were also confined to subjects for whom the brand was known for at least 75 per cent of their duration of smoking. Some analyses were further restricted to those for whom the brand was known for their entire duration of smoking. In general, the results from this group were similar to those from the 75 per cent group, which was larger, and we have chosen to report mostly on the latter.

To control confounding, we used multiple logistic regression (25). In addition to terms for values of tar exposure, indicator terms for the following variables were included in the logistic models: age, sex, ethnic group, geographic region, years of education, and year of interview. For the analyses confined to smokers, additional terms were included for number of cigarettes smoked per day and age at starting smoking. We tested trends in the relative risk estimates by entering ordinal terms with values corre-

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sponding to tar levels into the multivariate models.

RESULTS

A total of 614 of the 881 cases (70 per cent) and 852 of the 2,570 controls (33 per cent) were current cigarette smokers. As is shown in table 2, the estimated relative risk increased steadily with increasing number of cigarettes smoked per day, from 8.0 for the lightest smokers (<15 cigarettes/day) to 60 for the heaviest smokers (≥45 cigarettes/day). For ex-smokers, the estimate was 6.8. For any current smoking, it was 20.

Smokers were divided into three categories according to average tar content of cigarettes smoked. Relative risk estimates for the intermediate and highest tar categories compared with the lowest tar categories are displayed in table 3 for subjects for whom the brand smoked was known for at least 75 per cent of the total duration of smoking, and for the subset for whom the brand smoked was known for the entire duration of smoking (100 per cent). In each instance, the estimated risk increased with increasing tar content, although the estimates were somewhat lower for the 100 per cent subset: In the 75 per cent group, the estimate for the intermediate tar category compared with the lowest category was 1.9,

TABLE 2

Number of cigarettes smoked per day in relation to lung cancer risk, US and Canada hospitals, November 1981–June 1986

	Cases (n = 881)	Controls (n = 2,570)	Multivariate relative risk estimate	95% confidence interval
Never smoker	35	925	1.0*	
Ex-smoker	225	759	6.8	4.6–9.9
No. of cigarettes smoked/day				
<15	66	214	8.0	5.0–13
15–24	207	363	15	10–23
25–34	96	118	28	17–44
35–44	149	110	43	27–68
≥45	96	47	60	35–102
Unknown	7	34	6.1	2.2–17

* Reference category.

TABLE 3

Tar content of cigarettes smoked in relation to lung cancer risk, US and Canada hospitals, November 1981–June 1986

Av. tar content (mg/cigarette)	Cases	Controls	Multivariate relative risk estimate	95% confidence interval
Cigarette brand identified for at least 75% of years of smoking				
<22	35	142	1.0*	
22–28	95	88	1.9	1.0–3.7
≥29	40	23	3.1	1.3–7.1
Cigarette brand identified for all (100%) years of smoking				
<22	15	91	1.0*	
22–28	60	62	1.5	0.6–4.2
≥29	24	14	2.4	0.6–8.6

* Reference category.

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and for the highest tar category it was 3.1; the trend was significant ($\chi = 3.3$, $p = 0.001$). The corresponding estimates for the 100 per cent subset were 1.5 and 2.4, respectively ($\chi = 2.3$, $p = 0.02$). The remainder of the results reported here are based on the entire 75 per cent population of smokers.

Compared with never smokers, the relative risk estimates for smokers of the lowest, intermediate, and highest tar cigarettes were 11 (95 per cent confidence interval (CI) 5.9–19), 23 (95 per cent CI 14–38), and 36 (95 per cent CI 18–73), respectively.

Median tar values for the highest category were 31.1 mg/cigarette among cases and 31.6 mg/cigarette among controls, and the highest values were 34.0 and 34.1, respectively. The corresponding medians for the lowest categories were 19.1 and 18.6 mg/cigarette, and the lowest values were 15.3 and 9.1, respectively. No cases and six controls (2 per cent of the smokers in the 75 per cent population) had average tar values of less than 10 mg/cigarette.

As explained, average tar values were also computed separately for cigarettes smoked 10 or more years before hospital admission. The results are shown in table 4. There were fewer cases and controls in the lowest tar category and more in the highest tar category compared with the distributions based on all years of smoking. The relative risk estimates increased with increasing tar content, and were somewhat higher than the estimates based on all years of smoking: For smokers in the intermediate tar category, the estimate was 3.0 (compared with 1.9 from all years of smoking), and for those in the high tar category, it was 4.0 (compared with 3.1). The trend was statistically significant ($\chi = 3.1$, $p = 0.002$).

A further analysis was based on cigarettes smoked at least 20 years before hospital admission. The results were not materially different from those based on cigarettes smoked at least 10 years previously, and the remaining analyses are based on the latter period.

As is shown in table 5, the pattern of increasing risk with increasing tar level was broadly consistent by sex. Among men, the relative risk estimates for the intermediate and high tar categories were 3.6 and 4.0, respectively; the trend was on the borderline of statistical significance ($\chi = 2.0$, $p = 0.05$). Among women, the corresponding estimates were 1.8 and 4.7; this trend was significant ($\chi = 2.1$, $p = 0.04$).

The data for men and women were further stratified by number of cigarettes smoked per day. In most categories, the relative risk estimate tended to increase with increasing tar content. However, numbers were small and the results were not statistically significant (data not shown).

Discussion

The hypothesis that tar in cigarette smoke is a major component in the etiology of lung cancer has biologic plausibility (1) and is supported by some epidemiologic data (2, 3, 6, 7), although the magnitude of the association has tended to be modest. In addition, some results have been equivocal (4, 5). The results of the present large case-control study provide further evidence that the tar content of cigarette smoke is indeed

Table 4

Tar content of cigarettes smoked at least 10 years before admission in relation to lung cancer risk, US and Canada hospitals, November 1981–June 1986

Av. tar content (mg/cigarette)	Cases	Controls†	Multivariate relative risk estimate	95% confidence interval
<22	17	99	1.0*	
22–28	90	94	3.0	1.4–6.3
≥29	63	45	4.0	1.7–9.2

* Reference category.

† Fifteen controls had smoked for less than 10 years and are excluded from this analysis.

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TABLE 5

Tar content of cigarettes smoked at least 10 years before hospital admission in relation to lung cancer risk, by sex: US and Canada hospitals, November 1981–June 1986

Av. tar content (mg/cigarette)	Cases	Controls	Multivariate relative risk estimate	95% confidence interval
Men				
<22	7	32	1.0*	
22–28	68	48	3.6	1.2–11
≥29	44	23	4.0	1.2–13
Women				
<22	10	67	1.0*	
22–28	22	46	1.8	0.6–5.7
≥29	19	22	4.7	1.1–21

* Reference category.

related to lung cancer risk: We estimated that current smokers who had smoked cigarettes 10 or more years in the past with an average of at least 29 mg of tar per cigarette had approximately four times the risk of lung cancer as those who had smoked cigarettes with an average tar content of less than 22 mg. Smokers of cigarettes with intermediate tar content appeared to have a threefold increase in risk. The association was present in both men and women and did not appear to be accounted for by number of cigarettes smoked per day.

In interpreting the present results, we considered the possibility of distortion by various forms of bias. Selection bias seems unlikely: Lung cancer is an illness for which diagnosis and admission to hospital is almost inevitable and is certainly unrelated to the tar content of cigarettes smoked, especially in the distant past. The controls were selected to have diagnoses unrelated to smoking, some of which involved acute diseases requiring hospital admission. It is highly unlikely that among smokers these conditions would be related to tar content. It is conceivable that controls tended to underreport high tar smoking, or cases low tar smoking, producing a spurious association, but this does not seem likely. Potentially confounding factors were taken into account in estimating the relative risks, and included, in particular, the number of cigarettes smoked per day and the duration of smoking. Given the relatively uncomplicated etiology of lung cancer, it does not appear likely that there was uncontrolled confounding by factors not taken into account.

A weakness in our study was that we did not have complete lifetime histories of brands smoked for most subjects (since only the most recent and longest-smoked brands were obtained), nor were tar values available for all years. The assumptions that were made about the gaps in brand history, however, if incorrect, would have tended to underestimate average tar exposure, which would have led to underestimation of the relative risks. To minimize the effect of such assumptions, we confined the analysis to cases and controls for whom there was information covering at least 75 per cent of the duration of smoking; that is, tar values were assumed for not more than 25 per cent of the smoking history. This did result in the exclusion of a substantial proportion of subjects for whom there were larger gaps in the brand histories, but there is no reason to think that the population analyzed was biased with respect to tar values. We also analyzed the subset of cases and controls for whom there was brand information on the entire duration of smoking, and the results were similar to those for the 75 per cent population, although numbers (and the proportion of

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the total smoking population) were considerably smaller. The assumptions used to fill in the gaps in the tar values could also have resulted in underestimation of risks.

Another problem that could lead to underestimation of the effect of tar is that the results of this and other studies (2–5) were based on published tar values for cigarettes that were derived from standardized machine-smoking tests. It is well known that smokers of low nicotine cigarettes tend to compensate for lower nicotine by deeper inhalation or some other mechanism, thus minimizing differences in actual nicotine intake (26–29). Since nicotine and tar levels are correlated, this phenomenon would affect tar intake as well. To measure the true effect of tar, it would clearly be desirable to have a direct measure of tar intake. From the public health point of view, on the other hand, an advantage of the present analysis is that the effects of different cigarette brands as actually smoked were measured.

In this study, the relative risk point estimates for the different tar levels were somewhat higher when based on cigarettes smoked in the past than when based on all cigarettes, regardless of timing. This is plausible since, in terms of what is known about the carcinogenicity of substances such as benzo(*a*)pyrene, it might be expected that cigarettes smoked in the past are most etiologically relevant to lung cancer.

The present results add to the evidence suggesting that the tar content of cigarettes is associated with the risk of lung cancer. It should be remembered, however, that even smokers of the lowest tar cigarettes have a substantially increased risk—in this study, some 11-fold relative to those who never smoked. A related point that must also be emphasized is that this and previous studies lacked data on very low tar cigarettes. The median value in the lowest tar category was about 19 mg/cigarette, as against values of less than 10 mg/cigarette and even less than 5 mg/cigarette in some brands now available. Because of the long duration of smoking, there were very few subjects whose lifetime tar exposure averaged less than 10 mg/cigarette. Given the heavy marketing of such cigarettes with the implication that they are safer and given their widespread use, future studies should be focused on this gap in our knowledge.

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Compensation as a Risk Factor for Lung Cancer in Smokers Who Switch from Nonfilter to Filter Cigarettes

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Abstract: The likelihood of increasing the number of cigarettes per day (cpd), a common method of compensation, in smokers switching from nonfilter to filter cigarettes, was examined in newly diagnosed and histologically confirmed lung cancer cases including all cell types: 1,242 lung cancer cases and 2,300 sex and age matched hospital controls were interviewed in 20 hospitals from nine United States cities between 1969 and 1984.

The mean increase in cpd for lung cancer cases was about twice that of controls. Using switchers who did not increase cpd as the referent group, there was a linear dose-response relationship between the odds of lung cancer and increasing level of compensation. The odds ratio increased from 1.19 to 2.37 in males and from 1.66 to 3.83 in females corresponding to increases of 1–10 to 21+ cpd after switching.

Findings from this study suggest that increasing cpd after switching to filter cigarettes is an important risk factor for lung cancer that needs to be emphasized in epidemiologic studies. Proponents of the idea that switching cigarettes is of some benefit, should also advocate that individuals who continue smoking should avoid compensation after switching. (*Am J Public Health* 1989; 79:188–191.)

Introduction

Epidemiologic studies have shown a reduced risk for lung cancer among smokers who switch from nonfilter to filter cigarettes relative to those who continue smoking nonfilter cigarettes.[1] On the basis of this finding it has often been recommended that people who are unwilling or unable to give up smoking should switch to filter cigarettes. The tar intake per day after switching to filter cigarettes will be reduced if smokers continue to smoke the same or fewer numbers of cigarettes per day (cpd). In this paper the term "switchers" stands explicitly for smokers who switched from nonfilter to filter cigarettes. The ways by which switchers attempt to compensate for the reduction in nicotine are by increasing cpd or altering their puff frequency, puff duration, puff rate, and interpuff interval[2] exposing themselves to higher quantities of gas and particulate cigarette smoke constituents.[3] This study focuses on compensation in switchers who increase cpd among lung cancer cases and controls. The main questions of interest were: Is there a differential pattern of increase in cpd between cases and controls? Is there an increase in risk for lung cancer in switchers who increase cpd compared to those who do not?

Methods

The cases and controls in this study were interviewed between 1969 and 1984, in 20 hospitals in nine US cities, as part of a hospital-based ongoing study of smoking-related cancers.[4] In the original study, cases were patients with newly diagnosed and histologically confirmed tobacco-related cancers and controls were hospitalized patients with an admitting diagnosis consisting of conditions not thought to be related to smoking. non-neoplastic diseases. The smoking-related cancers excluded from control diagnoses were cancers of the oral cavity, larynx, nasopharynx, kidney, bladder, oesophagus, salivary gland, pancreas and liver; patients with heart disease, stroke, peripheral vascular disease, chronic bronchitis, emphysema, gastrointestinal ulcer, and cirrhosis were also excluded.

All study subjects were interviewed in the hospital by trained interviewers using a structured questionnaire that included sociodemographic variables, lifetime smoking history, cpd, brands of filter and nonfilter cigarettes smoked. For each individual, the average cpd of filter cigarettes was calculated by summing up the cpd for all filter brands and then dividing by the number of filter brands. The average cpd of nonfilter cigarettes was calculated similarly.

As a partial validation procedure, we checked the reliability of the initial smoking data by recontacting 100 cases and 100 controls, selected at random following their discharge from hospital.

In this investigation, only those who were current cigarette smokers and who had switched from nonfilter to filter cigarettes were considered. A current smoker was defined as someone who had smoked at least one cpd for a continuous period of one year or more and was also smoking within the year preceding diagnosis. Those cigarette smokers who smoked cigars or pipes concurrently were excluded. Cases were frequency matched at approximately a 1:2 ratio on sex and age at diagnosis (± 5 years) to controls.[5]

Statistical Techniques

All statistical analyses were performed separately by sex. Paired cpd data before and after switching were used to assess the change in cpd. Mean changes in cpd after switching for cases and controls were adjusted by linear regression for

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switch, and age at diagnosis), thereby facilitating simultaneous adjustment for the same potential confounders in multiple logistic models. In this paper, we restrict the term "compensation" to mean an increase in cpd after switching to filter cigarettes.

Multiple linear regression analysis[6] was performed among controls to determine if cpd after switching could be predicted by variables such as age at switching, nonfilter cpd, nonfilter duration, and tar yield per day before switching.

Results

A total of 781 male and 461 female lung cancer cases of all cell types and 1,432 male and 868 female controls were studied; all subjects were smokers who had switched to filter cigarettes. Among male switchers, 45 per cent (n = 351) of cases and 41 per cent (n = 580) of controls increased cpd; 42 per cent (n = 327) of cases and 44 per cent (n = 634) of controls smoked the same number of cpd; and 13 per cent (n = 103) of cases and 15 per cent (n = 218) of controls decreased cpd. Among female switchers, 59 per cent of cases (n = 272) and 48 per cent of controls (n = 418) increased cpd; 31 per cent (n = 143) of cases and 41 per cent (n = 356) of controls smoked the same number of cpd; and 10 per cent (n = 46) of cases and 11 per cent (n = 91) of controls decreased cpd.

The maximum reduction after switching among cases and controls was about 50 cpd in males and 60 cpd in females. The maximum increase noted ranged from 50–70 cpd in males and 50–60 cpd in females. In both males and females, the interquartiles (25th to 75th percentiles) ranged from 0–15 cpd in cases and 0–10 in controls.

Distributions of cases and controls by age, education, marital status, religion, and occupation are presented in Table 1. In both males and females, case-control differences were not evident in the sociodemographic variables. Mean ages at diagnoses for males were 57.0 years in cases and 56.1 years in controls. The corresponding ages for females were 56.8 years and 55.8 years.

Mean values of duration of smoking and cpd are shown in Table 2. On the average, both male and female cases had smoked nonfilter cigarettes 1.5–2 years longer than controls. In males, cases and controls smoked approximately the same duration of filter cigarettes while female cases smoked approximately one year longer than the controls. On the average, cases of both sexes smoked about 5 to 6 more cpd than the controls before switching, and about 8 more cpd than the controls after switching. Notably cases showed greater compensation than controls, the mean increase in cpd for cases being about twice that of controls. Adjustments for the differences between cases and controls in duration of nonfilter cigarette smoking, age at switching and age at diagnosis by analysis of covariance did not alter these results.

Mean values of cpd before and after switching by cpd classes before switching (1–10, 11–20, 21–30, 31–40 and 41+) are presented in Table 3. Three points are evident from these data. Most importantly, cases showed greater average compensation than the controls in each cpd class and the differences in compensation between cases and controls within classes were especially great for all the classes in males and for the first four classes in females. Compensation in cpd was evident only when the initial cpd was less than 30. When initial cpd was greater than 30, there was a tendency either not to increase or even to decrease cpd after switching. In both cases and controls, the extent of compensation progressively declined with increasing cpd before switching. The difference in cpd after adjustments using analysis of covariance for age at switching and duration of nonfilter cigarette smoking did not alter these results appreciably.

Table 4 shows a clearcut dose-response relationship for lung cancer with increasing cpd levels (compensation) in both

TABLE 1—Distribution of Demographic Variables among Cases and Controls

Demographic Variables	Males		Females	
	Cases N = 781 %	Controls N = 1432 %	Cases N = 461 %	Controls N = 868 %
Age (years)				
<44	7.8	8.8	10.2	10.6
45–54	29.1	33.2	27.8	31.5
55–64	42.1	41.5	41.2	40.9
65–74	19.6	15.2	18.2	15.7
75+	1.4	1.3	2.6	1.4
Education				
None, Grammar School	21.0	19.9	12.8	13.2
≤High School	24.5	24.0	25.0	21.3
High School Graduate	28.3	26.4	36.0	37.5
Some College	11.3	15.9	15.4	18.0
College	9.6	8.5	5.4	6.7
Postgraduate	5.4	5.3	3.5	3.3
Marital Status				
Single	6.0	7.7	6.7	6.3
Married	74.1	70.0	53.4	55.9
Divorced	9.5	13.0	12.2	12.0
Separated	4.4	4.3	4.3	5.7
Widowed	5.9	5.0	23.4	20.1
Religious Status				
Protestant	42.3	49.7	33.7	29.3
Catholic	43.8	34.5	44.1	36.7
Jewish	9.1	9.5	17.2	13.9
Other	2.2	3.2	3.0	3.4
None	2.6	3.2	2.0	1.2
Race				
Caucasian	85.2	81.8	91.5	85.6
Black	13.4	15.9	7.8	13.0
Hispanic	1.2	1.7	0.7	1.0
Oriental	0.3	0.4	0.0	0.2
Other	—	0.2	—	0.1
Occupation				
Professional	8.6	9.1	4.6	6.4
Business Executive	10.7	9.8	3.9	3.4
Technical	9.3	6.7	26.4	15.2
Clerical/Sales	21.2	20.4	8.3	12.7
Skilled	18.3	17.3	9.4	8.7
Semi-skilled	12.9	11.6	3.1	4.1
Unskilled	6.7	9.0	3.1	4.5
Retired/Unemployed	17.0	16.1	6.5	11.1
Housewife	—	—	34.9	34.0

TABLE 2—Mean Duration of Smoking and Cigarettes per Day (CPD) Smoked Before and After Switching among Cases and Controls

Total Number	Males		Females	
	Cases N = 781	Controls N = 1432	Cases N = 461	Controls N = 868
Mean Nonfilter duration in years (SE)	26.3 (0.4)	24.8 (0.3)	22.1 (0.6)	19.8 (0.4)
Mean Filter duration in years (SE)	13.5 (0.3)	13.0 (0.2)	15.6 (0.4)	14.3 (0.3)
Mean Nonfilter cpd (SE)	28.5 (0.5)	22.7 (0.3)	21.8 (0.5)	16.8 (0.3)
Mean Filter cpd (SE)	34.4 (0.6)	28.6 (0.4)	29.7 (0.6)	21.5 (0.4)
Difference in cpd[a] (SE)	5.9 (0.5)	3.9 (0.3)	7.8 (0.6)	4.7 (0.3)

[a]Difference in cpd = Filter cpd − Nonfilter cpd.
SE = Standard Error

Table 4 shows a clearcut dose-response relationship for lung cancer with increasing cpd levels (compensation) in both

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TABLE 3—Mean Cigarettes per Day (CPD) Smoked Before and After Switching According to Nonfilter CPD Groups

	Nonfilter cpd in Males									
	1–10		11–20		21–30		31–40		41+	
	Cases n = 42	Controls n = 212	Cases n = 324	Controls n = 786	Cases n = 174	Controls n = 208	Cases n = 158	Controls n = 163	Cases n = 74	Controls n = 57
Mean Nonfilter cpd (SE)	8.4 (0.4)	7.9 (0.2)	19.3 (0.1)	19.1 (0.1)	28.4 (0.2)	28.5 (0.2)	39.2 (0.2)	39.5 (0.1)	57.2 (1.0)	57.5 (1.3)
Mean Filter cpd (SE)	19.1 (1.9)	14.7 (0.7)	27.6 (0.7)	24.2 (0.4)	35.2 (1.0)	33.1 (0.8)	42.6 (1.1)	38.4 (1.2)	53.5 (2.1)	46.7 (2.5)
Difference in cpd[a] (SE)	10.7 (1.9)	6.8 (0.7)	8.2 (0.7)	5.0 (0.4)	6.7 (1.0)	4.6 (0.8)	3.3 (1.1)	−1.1 (1.2)	−3.7 (1.9)	−10.8 (2.3)
	Nonfilter cpd in Females									
	n = 87	n = 308	n = 241	n = 446	n = 72	n = 60	n = 39	n = 35	n = 20	n = 13
Mean Nonfilter cpd (SE)	8.4 (0.3)	7.6 (0.2)	19.0 (0.2)	18.6 (0.1)	28.0 (0.3)	28.3 (0.3)	39.1 (0.3)	39.0 (0.4)	56.9 (2.4)	58.5 (2.1)
Mean Filter cpd (SE)	22.4 (1.2)	14.5 (0.5)	27.1 (0.7)	22.9 (0.4)	35.3 (1.2)	31.7 (1.3)	42.5 (1.6)	36.6 (2.2)	45.7 (3.5)	49.7 (5.6)
Difference in cpd[a] (SE)	14.1 (1.3)	6.9 (0.5)	8.0 (0.7)	4.2 (0.4)	7.3 (1.2)	3.3 (1.3)	3.4 (1.6)	−2.4 (2.2)	−11.2 (4.5)	−8.8 (6.6)

[a]Difference in cpd = Filter cpd − Nonfilter cpd.

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sexes. The odds ratios increased from 1.19 to 2.37 in males and 1.66 to 3.83 in females corresponding with increases of 1–10 to 21+ cpd after switching.

The odds ratio associated with increasing cpd versus decreasing cpd after switching, relative to those who did not change cpd, was also examined. Compared to those who did not change their cpd, those who increased cpd had an odds ratio of 1.38 (95 per cent confidence intervals = 1.31, 1.69) in males and 2.19 (95 per cent CI = 1.67, 2.89) in females after adjusting for confounders. In contrast, males who decreased cpd had a reduction in the odds ratio to 0.64 (95 per cent CI = 0.47, 0.86); in females, the number of cases who decreased cpd was small (n = 46) and the corresponding odds ratio was 0.97 (95 per cent CI = 0.62, 1.55).

Since greater compensation occurred among those who initially smoked ≤30 cpd (Table 3), we examined the risks associated with increasing cpd according to those who initially smoked ≤30 cpd and >30 cpd. Among those who initially smoked ≤30 cpd, those who increased cpd had elevated odds ratios of 1.34 (95 per cent CI = 1.08, 1.65) in males, and 1.84 (95 per cent CI = 1.42, 2.38) in females for lung cancer, relative to those who did not increase cpd, after adjustments for age at switch, duration of nonfilter and filter cigarette smoking. Among those who initially smoked >30 cpd, the corresponding odds ratio was also elevated in males: OR = 1.67 (95 per cent CI = 1.08, 2.57); in females, OR = 0.94 (95 per cent CI = 0.37, 2.41); the numbers of cases (n = 59) and controls (n = 48) were relatively small.

The regression of compensation (filter cpd − nonfilter cpd) on nonfilter cpd yielded negative slopes, indicating that nonfilter cpd was a negative predictor of compensation, i.e., the lower the initial cpd, the greater the compensation.

Linear regression analysis among controls was performed to examine the effect of selected variables in predicting cpd after switching. Results were similar for males and females. Cigarettes per day before switching (β = 0.7, S.E. = 0.03) and age at switching (β = 0.2, S.E. = 0.03) predicted cpd after switching in linear regression models. These variables together accounted for 34 per cent and 39 per cent of the variability among males and females, respectively, while duration of nonfilter cigarette smoking, tar yield per day before switching, and age at start of smoking accounted for little or none of the variability.

TABLE 4—Logistic Regression Analysis Results Showing Risks of Lung Cancer for Those Who Increased CPD after Switching

Increase in Filter CPD	Cases	Controls	Odds Ratio[ab]	95% Confidence Interval
Males				
Did not increase cpd[c]	430	852	1.00	—
1–10 vs did not increase cpd	150	326	1.19	0.93–1.51
11–20 vs did not increase cpd	128	180	1.75	1.33–2.29
21+ vs did not increase cpd	72	70	2.37	1.64–3.41
Females				
Did not increase cpd[c]	189	447	1.00	—
1–10 vs did not increase cpd	126	262	1.66	1.23–2.24
11–20 vs did not increase cpd	101	115	2.97	2.09–4.20
21+ vs did not increase cpd	45	40	3.83	2.31–6.34

[a]Adjusted for nonfilter duration, filter duration, nonfilter cpd, and age at switch.
[b]Test of linear trend significant at $p < 0.05$.
[c]Referent category.

Discussion

The results of this study indicate that a sizable portion of smokers tend to compensate (increase cpd) after switching from nonfilter to filter cigarettes and that patients with lung cancer compensate more than controls. A greater proportion of females (50–60 per cent) than males (40–45 per cent) showed compensation in cpd. Among switchers who increased cpd, there was a linear dose-response relation between the odds of lung cancer with increasing level of compensation. The linearity of the dose response pattern in both sexes supports the biological plausibility of compensation as an important risk factor for lung cancer. We emphasize that these results are adjusted for past smoking patterns and duration differences.

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In our study, the lower the initial cpd, the greater the tendency to compensate by increasing cpd. In fact, heavy smokers of nonfilter cigarettes (>30 cpd) on the average tended to decrease rather than increase cpd after switching to filter cigarettes. There may be several explanations for this finding. It is possible that heavy smokers may compensate by altering their smoking topography since there may be a time limitation (less leeway) in smoking additional cigarettes and/or encumbent symptoms might compel them to smoke less upon switching. A similar finding was noted in the 13-year follow-up survey by the American Cancer Society.[9] Lighter smokers (not separated by switch status) of less than half a pack a day in 1959 showed an average increase in cpd by 1972 which doubled that observed in heavier smokers. Another plausible explanation relates to an upper threshold phenomenon of nicotine dependency. In the already heavy nonfilter cigarette smokers (>30 cpd), the amount of filter cigarettes smoked (even when it is less than the initial cpd) after switching may be sufficient to maintain their required nicotine level.

One possible source of bias in this study is recall bias. If cases overestimated their exposure, while controls underestimated it, then the risk will appear larger than real. As a partial validation procedure, we reinterviewed 100 cases and 100 controls following their discharge from hospital. The results from the second interview showed good agreement with first reported cpd in both groups (average correlation 0.90) and revealed no differential reporting between cases and controls. The average difference between first and second interviews for both cases and controls was only one cpd.

The major reason for limiting our analysis to switchers only was to facilitate adjustment for the corresponding sets of confounders (duration of nonfilter smoking, age at switch, and duration of filter smoking) within the comparison groups, i.e., switchers who did not compensate, using multiple logistic analysis. Since there is also intense interest in comparing switchers with exclusive nonfilter cigarette smokers, we attempted to assess their patterns of odds ratio. Wynder and Kabat[10], observed minimum odds ratios for lung cancer of 0.66 and 0.74 in males and females, respectively, among switchers who had smoked filter cigarettes for more than 10 years, relative to exclusive nonfilter smokers. Assuming that 0.66 and 0.74 represent the odds ratios among male and female switchers who increased by 1–10 cpd after switching (this was the median class of cpd change in our study), we computed odds ratios due to various levels of compensation relative to nonfilter cigarette smokers (Figure 1). Further reductions in odds ratios are evident with no compensation (0.55 and 0.45 in males and females, respectively), whereas for switchers who compensate, the odds ratios increase in a linear fashion, and even become greater than that of nonfilter only smokers when the compensation level exceeds 20 cpd.

Compensation as a risk factor has not been stressed in epidemiologic studies comparing the health risk of nonfilter to filter cigarette switchers relative to exclusive nonfilter cigarette smokers. Compensation is undoubtedly a complex phenomenon. It includes changes in puff frequency, duration, rate and interval[2]. Nevertheless, the relatively simple measure of compensation used in this study (increase in cpd after switching) has proved to be an important risk factor for lung cancer in itself. Based on our results, the lung cancer risk among smokers who switch to filter cigarettes would be reduced further if they strive not to increase cpd after switching. Proponents of the idea that switching cigarettes is of some benefit should also advocate that individuals who continue smoking should avoid compensating after switching.

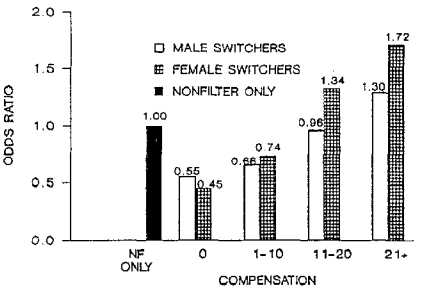

FIGURE 1—Risks among Switchers Relative to Nonfilter Only Smokers According to Different Levels of Compensation.*

**Compensation is the increase in cigarettes per day after switching to filter cigarettes.*

SOURCE: Computed from the results of this study and the results of the study by Wynder and Kabat[10].

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Changes in patterns of cigarette smoking and lung cancer risk: results of a case–control study

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Summary Data from a case–control study on lung cancer were used to evaluate how changes in cigarette habits, mainly smoking cessation, switch from non-filter to filter brands, from dark to light tobacco, or from handrolled to manufactured cigarettes, and reduction in daily consumption influence lung cancer risk. The results presented concern all males, exclusive cigarette smokers, involved in the study, i.e. 1,057 histologically confirmed lung cancer and 1,503 matched controls. The general decrease in lung cancer risk with the years since cessation was also found in each subgroup of cigarette exposure defined by duration of smoking, daily consumption and type of cigarettes smoked. Among smokers who had given up smoking from less than 10 years earlier, the lung cancer risks were two-fold higher for those who had stopped smoking for coughing or health reasons than for those who had stopped smoking for reasons other than health problems. A decrease in lung cancer risk, although not significant, was found in people who switched from non-filter brands to filter brands and from dark to light tobacco and in smokers who reduced their daily consumption of cigarettes by more than 25% as compared to smokers who had not changed habits.

The epidemiological evidence on smoking-related factors that modify the incidence of lung cancer was recently summarised (US Surgeon General, 1982; IARC, 1986). The excess of risk is much higher for cigarette smokers than for smokers of other types of tobacco; for cigarette smokers, lung cancer risk increases with daily consumption and with duration of smoking and decreases with time since smoking cessation. In recent epidemiological studies, there was a tendency for lung cancer risks to be lower among users of filter than of non-filter cigarettes and among low-tar cigarette smokers as opposed to high-tar cigarette smokers. Moreover, an excess of lung cancer risk for lifetime dark tobacco smokers as compared to lifetime light tobacco smokers was reported.

We report here how changes in cigarette habits, mainly smoking cessation, switch from non-filter to filter brands, from dark to light tobacco, or from handrolled to manufactured cigarettes, and reduction in daily consumption influence lung cancer risk.

Materials and methods

An epidemiological study on lung cancer was conducted simultaneously in five European countries with the support of the US National Cancer Institute to compare the role of different smoking habits in the causation of lung cancer, especially the use of filter cigarettes and the type of tobacco (light or dark, hand-rolled or manufactured). Methods for collecting the data and some results have been given in previous reports on French data (Benhamou *et al.*, 1985, 1986, 1987) and on the international data as a whole (Lubin *et al.*, 1984*a*, *b*, *c*). In France, a total of 1,625 cases with histologically confirmed lung cancer and 3,091 controls matched on sex, age at diagnosis (± 5 years), hospital of admission and interviewer were included in the study.

The results reported here concern all French males who had smoked only cigarettes at some time of their lives. The subgroup which has been extracted for the original study includes all male strata in which the case and one (or both) control(s) were cigarette smokers, so that matching was respected. Among the 1,514 male strata, 244 were excluded because either the case or both controls were smokers but not exclusive cigarette smokers. Of the 1,270 remaining strata, 32 were excluded because the case was a non-smoker and 181 were excluded because none of the matched controls was a cigarette smoker. Consequently, the presented results concern 1,057 strata (1,057 cases and 1,503 matched controls). We reported in a previous paper (Benhamou *et al.*, 1986) lung cancer risks of smokers versus non-smokers. The risk associated with exclusive cigarette smoking was 13.3 times that associated with non-smoking.

Of the 1,057 cases, 82% were in Kreyberg I category (epidermoid, small-cell or large-cell carcinomas), and 9% in Kreyberg II category (adenocarcinoma). For each smoker, the four most recent cigarette brands usually smoked and, for each, the daily consumption and the duration of smoking were recorded. From the four brands of cigarettes smoked, smokers were then classified in three categories (Benhamou *et al.*, 1985): the first comprised those having always smoked filter cigarettes, the second those having smoked filter and non-filter cigarettes ('mixed') and the last those having never smoked anything but non-filter cigarettes. Similar classifications were used for the type of tobacco smoked and for the use of manufactured or handrolled cigarettes. In addition, the causes of stopping smoking and of a switch from non-filter to filter brands were, if relevant, recorded.

Analytical method

The data were analysed using the PIGAS program (Wartelle *et al.*, 1983). Matched relative risks (RR) of lung cancer and their 95% confidence intervals (CI) were derived from logistic regressions which allow estimations of RR associated with each variable when adjusting for the others. We used matched logistic regression (Breslow & Day, 1980) whenever possible and otherwise adjusted RR and 95% CI were estimated with the Mantel–Haenszel method (Mantel, 1963).

Results

Smoking cessation

Although most of the male life-long cigarette smokers included in the study were still smoking at the time of interview, the percentage of ex-smokers was significantly lower ($P < 0.0001$) among cases (26%) than among controls (36%) (Table I). Matched RR of lung cancer among ex-smokers as compared to current smokers, adjusted for duration of smoking and daily consumption of cigarettes, dropped sharply after their having stopped smoking and was dependent on the number of years since cessation (trend test $P < 0.0001$). However, relative to current smokers, a significant excess of risk was found for smokers who had given up smoking from between 1 and 4 years earlier (RR = 1.5, $P < 0.01$). Never-

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Table I Matched relative risks of lung cancer by years since cigarette cessation

Years since cigarette cessation	No (%) of cases	No (%) of controls	Matched RR[a]	95% CI
0	776 (74)	969 (64)	1.0[b]	
1–4	154 (15)	138 (9)	1.5[c]	1.1 1.9
5–9	66 (6)	120 (8)	0.7	0.5 1.0
10–19	42 (4)	147 (10)	0.5[c]	0.3 0.8
⩾20	19 (1)	129 (9)	0.4[c]	0.2 0.8

[a]Adjusted for duration of smoking and daily consumption of cigarettes. Trend test $P<0.001$. [b]Current smokers. Risk for people who had never smoked relative to this baseline category was 0.1. [c]$P<0.01$.

theless, even after 20 years or more of not smoking, the lung cancer risk remained 4-fold higher ($P<0.001$) than that of life-long non-smokers. Similar decrease of the risk was observed in either Kreyberg I or Kreyberg II categories.

Table II shows lung cancer risks by reasons for stopping smoking, adjusted for daily consumption and duration of smoking. Among smokers who had given up smoking less than 10 years earlier, lung cancer risks were 2-fold higher for those who had stopped smoking for coughing or health reasons than for those who had stopped smoking for reasons other than health problems. On the contrary, the risks were similar whatever the reasons after 10 years or more cessation.

Relative risks of lung cancer have been estimated according to the number of years since cessation for different variables of cigarette exposure (Table III). For each class of the different variables considered (duration of smoking, daily consumption and type of cigarettes smoked) a decrease in lung cancer risk was found with the years since cessation, except for smokers who gave up smoking from between 1 and 4 years earlier. Considering duration of smoking, after 20 years or more of not smoking, the risk of lung cancer among men who had smoked for 1–25 years dropped to 20% of that for men who continued to smoke and the risk remained 2-fold higher than that for life-long non-smokers. In longer-term smokers, for example men who had smoked for more than 35 years, the risk was still 33% of that of current smokers, even after 20 years or more of not smoking. Considering the daily consumption, after 20 years or more of not smoking, the lung cancer risk among men who had smoked one to nine cigarettes per day dropped to 50% of that for men who continued to smoke and to 25% among men who had smoked 20 cigarettes per day relative to current smokers. Similar results were observed considering the type of cigarette.

Table II Relative risks (95% CI) of lung cancer by years since cigarette cessation and reasons for stopping smoking

Reasons for stopping smoking[a]	Years since cigarette cessation			
	1–4	5–9	10–19	⩾20
No health reasons	1.0	0.5(0.3–1.0)	0.5(0.3–1.2)	0.5(0.2–1.2)
Cough or health reasons	2.2(1.3–3.5)[b]	1.1(0.6–1.9)	0.5(0.3–1.0)	0.5(0.2–1.3)

[a]Adjusted for daily consumption and duration of cigarette smoking. [b]$P<0.01$.

Changes in type of cigarette smoked

Among 'mixed' smokers, we only studied lung cancer risks in people who switched from non-filter to filter cigarettes, from dark to light tobacco and from handrolled to manufactured cigarettes. Two classes of smokers were defined to take into account the proportion of years of non-filter, dark or handrolled cigarette use. Table IV shows the lung cancer risks by change in type of cigarettes smoked, adjusted for daily consumption and duration of cigarette smoking. The risks decreased significantly for life-long filter cigarette smokers as compared to life-long non-filter cigarette smokers (RR = 0.7, $P<0.01$) and for life-long light tobacco users as compared to life-long dark tobacco users (RR = 0.3, $P<0.0001$). Similarly, lung cancer risk was decreased, although not significantly, for life-long manufactured cigarette smokers as compared to life-long handrolled cigarette smokers (RR = 0.8). The risks for 'mixed' smokers were generally intermediate between the extreme categories, but not significantly different from the reference category.

Reduction in daily consumption

In order to study the risk patterns as related to changes in the number of cigarettes smoked per day, the relative variation of cigarette consumption was calculated for each smoker

Table III Relative risks (95% CI) of lung cancer by years since cigarette cessation and different smoking habits

	Years since cigarette cessation				
	0	1–4	5–9	10–19	⩾20
Smoking duration (years)[a]					
1–25	1.0	1.0(0.4–2.2)	1.0(0.4–2.1)	0.1(0.1–0.4)	0.2(0.1–0.4)[f]
26–35	1.6(1.2–2.3)[b]	1.8(1.1–3.0)	0.8(0.4–1.5)	1.0(0.5–1.8)	0.9(0.4–2.2)
⩾36	2.1(1.5–2.9)[f]	3.1(2.0–4.7)[f]	1.4(0.8–2.4)	1.2(0.6–2.3)	0.7(0.2–2.4)
Cigarettes per day[b]					
1–9	1.0[d]	3.3(1.3–8.8)	0.5(0.1–2.4)	0.9(0.3–2.8)	0.5(0.1–4.1)
10–19	2.4(1.6–3.6)[f]	3.8(2.2–6.8)[f]	1.5(0.7–3.2)	1.0(0.4–2.3)	2.0(0.7–6.2)
⩾20	5.2(3.5–7.6)[f]	5.8(3.6–9.2)[f]	3.4(2.0–5.8)[f]	1.9(1.1–3.5)	1.3(0.3–5.1)
Type of cigarettes[b]					
Light	1.0[e]	0.7(0.1–3.9)	0.7(0.1–3.6)	0.5(0.1–5.0)	0.4(0.1–2.8)
Mixed	2.0(0.9–4.2)	5.0(1.7–15)[h]	2.1(0.5–7.9)	1.6(0.4–6.3)	2.5(0.4–16.7)
Dark	2.5(1.3–5.1)	3.3(1.6–6.9)[h]	1.8(0.8–3.8)	1.0(0.4–2.2)	0.8(0.3–2.1)
Filter	1.0[f]	1.4(0.7–3.1)	1.3(0.4–4.8)	0.6(0.4–0.9)	0.3(0.3–1.9)
Mixed	1.8(1.3–2.5)[f]	2.1(1.2–3.6)[h]	1.4(0.8–2.5)	0.6(0.2–1.4)	0.8(0.2–4.1)
Non-filter	1.9(1.4–2.5)[f]	2.7(1.8–4.0)[f]	1.1(0.7–1.8)	0.6(0.4–1.0)	0.5(0.3–1.0)
Manufactured	1.0[g]	1.3(1.0–1.7)	0.6(0.4–0.9)[h]	0.4(0.3–0.6)[f]	0.3(0.2–0.6)[f]
Mixed	1.2(0.9–1.6)	1.8(0.9–3.3)	1.7(0.7–4.1)	1.4(0.4–4.7)	0.4(0.1–1.7)
Handrolled	1.2(0.8–1.7)	4.6(1.8–12)[h]	1.0(0.4–2.3)	0.2(0.1–0.7)	0.1(0.0–0.7)

[a]Adjusted for age and daily consumption of cigarettes. [b]Adjusted for age and duration of cigarette smoking. [c]Current smokers who had smoked 1–25 years. Risk for people who had never smoked relative to this baseline category was 0.12. [d]Current smokers who had smoked 1–9 cigarettes per day. Risk for people who had never smoked relative to this baseline category was 0.25. [e]Current smokers who had smoked light tobacco. Risk for people who had never smoked relative to this baseline category was 0.18. [f]Current smokers who had smoked filter cigarettes. Risk for people who had never smoked relative to this baseline category was 0.12. [g]Current smokers who had smoked manufactured cigarettes. Risk for people who had never smoked relative to this baseline category was 0.07. [h]$P<0.01$, [i]$P<0.001$.

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Table IV Relative risks of lung cancer by change in type of cigarette smoked

Type of cigarette smoked	No. (%) of cases	No. (%) of controls	RR[a]	95% CI
Always non-filter	665 (64)	917 (62)	1.0[b]	
Non-filter to filter				
51–99% non-filter	209 (20)	245 (17)	1.0	0.8–1.3
1–50% non-filter	57 (6)	104 (7)	0.8	0.5–1.1
Always filter	99 (10)	212 (14)	0.7	0.5–0.9
Always dark	954 (95)	1296 (91)	1.0[c]	
Dark to light				
51–99% dark	28 (3)	34 (2)	1.0	0.1–8.2
1–50% dark	10 (1)	20 (2)	0.7	0.3–1.6
Always light	15 (1)	74 (5)	0.3	0.2–0.6
Always handrolled	89 (9)	110 (8)	1.0[d]	
Manufactured to handrolled				
51–99% handrolled	55 (5)	58 (4)	1.1	0.6–2.2
1–50% handrolled	54 (5)	52 (3)	1.1	0.4–2.6
Always manufactured	833 (81)	1255 (85)	0.8	0.6–1.1

[a]Adjusted for age, duration of cigarette smoking and daily consumption of cigarettes. [b]Life-long non-filter cigarette smokers. Risk for people who had never smoked relative to this baseline category was 0.08. [c]Life-long dark tobacco smokers. Risk for people who had never smoked relative to this baseline category was 0.08. [d]Life-long handrolled cigarette smokers. Risk for people who had never smoked relative to this baseline category was 0.07.

(for people who had smoked more than two brands of cigarettes during their smoking life, it was calculated from the number of cigarettes of the most recent and of the first brand). Two per cent of the smokers were excluded from the analysis because they increased and then reduced their consumption (or *vice versa*). A total of 1,027 cases and 1,481 controls were included in the analysis. Of these smokers, 51% had smoked one brand of cigarettes, 40% two brands, 8% three brands and 1% four brands. Table V shows the relative risks, adjusted for duration of smoking and daily consumption of the earlier brand, by changes in number of cigarettes each day. Of the 1,027 cases, 72% had not changed, 18% reported an increase and 10% reported a decrease (3% had reduced their consumption by less than 25%, 4% by 26–50% and 3% by more than 50%). Of the 1,481 controls, the figures were respectively 76%, 15% and 9% (2% had reduced their consumption by less than 25%, 4% by 26–50%, and 3% by more than 50%). A significant excess of lung cancer risk was found for smokers who reported an increase in daily consumption (RR = 1.4, $P < 0.01$). A decrease in risk, although not significant, was observed in people who reduced their daily consumption by more than 25%, as compared to smokers who had not changed habits (RR = 0.8).

Table V Relative risks of lung cancer by change in daily consumption of cigarettes

Change in daily consumption	No. (%) of cases	No. (%) of controls	RR[a]	95% CI
None	739 (72)	1118 (76)	1.0[b]	
Increased	187 (18)	215 (15)	1.4[c]	1.1–1.7
Decreased				
1–25%	29 (3)	37 (2)	1.1	0.4–3.0
26–50%	42 (4)	65 (4)	0.8	0.5–1.2
>50%	30 (3)	46 (3)	0.8	0.4–1.3

[a]Adjusted for age, duration of smoking and daily consumption of the earlier brand. [b]Smokers who had not changed their daily consumption. Risk for people who had never smoked relative to this baseline category was 0.08. [c]$P < 0.01$.

Discussion

In our study, lung cancer risk of ever smokers, although decreasing with the number of years since smoking cessation, remains 4-fold higher, even after 20 years or more of not smoking, than that of non-smokers. This result is consistent with those reported in two cohort studies (Doll & Peto, 1976; Rogot & Murray, 1980) but not in two other cohort studies (Hammond, 1966; Cederlof *et al.*, 1975) in which the risk of developing lung cancer after 10 years since smoking cessation approached that of non-smokers.

The increased risk of lung cancer among smokers who had given up smoking between 1 and 4 years earlier as compared to current smokers is usually explained by the fact that not only healthy but also sick individuals quit smoking (Surgeon General, 1979). The increased risk for health reasons is observed only among those who stopped smoking less than 10 years earlier, suggesting that lung cancer specific symptoms occur mainly in the 10 years before onset of the disease.

The slope of the decrease of lung cancer risk is similar in each class of characteristics of cigarette exposure (i.e. duration of smoking, life-long daily consumption and type of cigarette smoked). Consequently, as there is a direct relationship between daily consumption and lung cancer risk, after 20 years or more since smoking cessation, smokers who had a low daily consumption were at lower risk of lung cancer than smokers who had a greater daily consumption. Similarly, after 20 years or more since smoking cessation, a lower lung cancer risk was found for short-term smokers than for longer-term smokers.

In a previous paper, we reported a more harmful effect of dark than light tobacco, of non-filter than filter cigarettes, and of handrolled than manufactured cigarettes. This more harmful effect remained after smoking cessation: after 20 years of not smoking, the lung cancer risk remained 2-fold higher in people who had smoked only dark tobacco than in people who had smoked only light tobacco. Similarly, an excess of risk was found, after 20 years or more of not smoking, for exclusive smokers of non-filter cigarettes as compared to exclusive smokers of filter cigarettes (RR = 1.7). However, the reductions of risk among smokers who switched either from dark to light tobacco or from non-filter to filter cigarettes were not significant. These results could be due to the small number of smokers who changed in our study. However, in the international study (Lubin *et al.*, 1984), in which a large number of cases and controls had switched from non-filter to filter brands, no significant decrease in lung cancer risk was found.

In conclusion, among possible modifications in cigarette exposure, smoking cessation is responsible for the most important decrease in lung cancer risk. The other modifications of smokers' behaviour (switch from non-filter to filter cigarette, or from dark to light tobacco, and reduction in daily consumption) lead to a non-significant decrease of the risk, probably due to a lack of power.

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COMPENSATION AS A RISK FACTOR FOR LUNG CANCER IN SMOKERS WHO SWITCH FROM NONFILTER TO FILTER CIGARETTES

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ABSTRACT

The likelihood of increasing the number of cigarettes per day (cpd), a common method of compensation, in smokers who had switched from nonfilter to filter cigarettes was examined in newly diagnosed and histologically confirmed lung cancer cases including all cell types. There were a total of 1242 lung cancer cases and 2300 sex and age matched hospital controls interviewed in twenty hospitals from nine United States cities between 1969 and 1984.

Lung cancer cases compensated more (as increased cpd after switching) than the controls. The mean increase in cpd for cases was about twice that of controls. Using switchers who did not increase cpd as the referent group, switchers who increased cpd showed a clearcut dose-response relationship for lung cancer with increasing levels of compensation. The odds ratio increased from 1.2 to 2.4 in males and 1.7 to 3.8 in females corresponding to increases of 1-10 to 21+ cpd after switching.

Findings from this study suggest that increasing cpd after switching to filter cigarettes is an important risk factor for lung cancer that needs to be stressed in epidemiologic studies. Proponents of the idea that switching cigarettes is of some benefit, should also advocate that individuals who continue smoking should avoid compensation after switching.

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INTRODUCTION

A reduced risk for lung cancer has been observed among those who use filter versus nonfilter cigarettes (IARC, 1986). On the basis of this finding it has been often recommended that people who are unwilling or unable to give up smoking should switch to filter cigarettes. Since filter cigarettes generally have reduced tar per cigarette, switchers (in this paper the term switchers explicitly stands for smokers who switched from nonfilter to filter cigarettes) will have reduced tar intake per day if they smoke the same number of cigarettes per day (cpd) as before or smoke less. In general, smokers may increase cpd with years of smoking. However, among switchers, the likelihood of increasing cpd after switching to filter cigarettes appears to be mainly due to "compensatory" smoking. This study is focused on switchers who compensate by increasing cpd among lung cancer cases and controls. It examines the smoking habits of switchers and characterizes the changes which differentiate lung cancer cases from controls. The main questions of interest were : Do smokers generally increase cpd after switching to filter cigarettes? If so, is there a differential pattern of increase in cpd between cases and controls? Is there an increase in risk for lung cancer in switchers who increase cpd compared to those who do not increase cpd?

METHODS

The cases and controls (20-80 years of age) were interviewed between 1969 and 1984, in twenty hospitals in nine U.S. cities, as part of a hospital-based ongoing study of smoking-related cancers (Wynder and Stellman, 1977). Cases were patients with newly diagnosed and histologically confirmed lung cancer. Controls had cancers of other organs and non-neoplastic dieases not associated with tobacco use. The exclusion of smoking-related conditions from control diagnoses was intended to reduce potential bias in the assessment of risks due to cigarette smoking. The smoking-related cancers excluded from control diagnoses were cancers of the oral cavity, larynx, nasopharynx, kidney, bladder, esophagus, salivary gland, pancreas and liver as well as heart disease, stroke, peripheral vascular disease, chronic bronchitis, emphysema, gastrointestinal ulcer, and cirrhosis. For the purpose of this study, only current cigarette

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smokers and those who had switched from nonfilter to filter cigarettes were considered. A current smoker was defined as someone who had smoked cigarettes only for a continuous period of one year or more and was also smoking within the year preceding diagnosis. Controls were frequency matched at an approximate 2:1 ratio on sex and age at diagnosis (± 5 years) to cases (Kelsey, 1986). All study subjects were interviewed in the hospital by trained interviewers using a structured questionnaire which included sociodemographic variables and lifetime smoking history. Information about the age at which the subject began smoking, cpd, brands of filter and nonfilter cigarettes smoked, and number of years of smoking each brand, was obtained. For each individual, the average cpd of filter cigarettes was calculated by summing up the cpd for all filter brands and then dividing by the number of filter brands. The average cpd of nonfilter cigarettes was calculated similarly.

Statistical Techniques: All statistical analyses were performed separately by sex. The change in cpd after switching was assessed by analysis of the paired data. Mean changes in cpd after switching for cases and controls were adjusted (by linear regression) for age at switching and duration of nonfilter cigarette smoking utilizing analysis of covariance (Snedecor and Cochran, 1974). Adjusted means for cases and controls were compared by t-tests using the error mean square from the analysis of covariance with the appropriate degrees of freedom (Freund and Littel, 1981, Snedecor and Cochran, 1974).

Logistic regression analysis (Breslow and Day, 1980) was used to estimate the odds ratio for lung cancer in those who compensated, relative to those who did not compensate, with adjustments for various confounders such as nonfilter cpd, duration of nonfilter and filter cigarette smoking, and age at dignosis or age at switching. In this paper, we restrict the term "compensation" to the increase in cpd after switching to filter cigarettes.

RESULTS

A total of 781 male and 461 female lung cancer cases of all cell types and 1432 male and 868 female controls who were switchers were available for study. Among male switchers, 45% (n=351) of cases and 41% (n=580) of controls

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increased cpd, 42% (n=317) of cases and 44% (n=634) of controls smoked the same number of cpd, and 13% (n=103) of cases and 15% (n=218) of controls decreased cpd. Among female switchers, 59% of cases (n=272) and 48% of controls (n=418) increased cpd, 31% (n=143) of cases and 41% (n=356) of controls smoked the same number of cpd and 10% (n=46) of cases and 11% (n=91) of controls decreased cpd.

Distributions of cases and controls by age, education, marital status, religion and occupation were examined. In both sexes, case-control differences were not evident in the sociodemographic variables. Mean ages at diagnoses for males were 57.0 years in cases and 56.1 years in controls. The corresponding ages for females were 56.8 years and 55.8 years. In both sexes, the interquartiles (25th to 75th percentiles from univariate analysis) for the changes in cpd ranged from 0–15 cpd in cases and 0–10 in controls.

Mean values of cpd before and after switching and the mean change in cpd among cases and controls are presented in Table 1. On the average, cases of both sexes smoked about 5 to 6 more cpd than the controls before switching, and about 8 more cpd than the controls after switching. Notably, cases showed significantly greater compensation than controls. The mean increase in cpd for cases was about twice

TABLE 1

MEAN CIGARETTES PER DAY (CPD) SMOKED BEFORE AND AFTER SWITCHING AMONG CASES AND CONTROLS

	MALES		FEMALES	
	Cases	Controls	Cases	Controls
Total	781	1432	461	868
Nonfilter cpd	28.5	22.7	21.8	16.8
Filter cpd	34.4	26.6	29.7	21.5
Change in cpd (Filter − Nonfilter)	5.9*@	3.9*	7.8*@	4.7*

* Denotes significant deviation from 0 at $p < 0.001$.
@ Mean change in cpd for cases differed from controls at $p < 0.001$.

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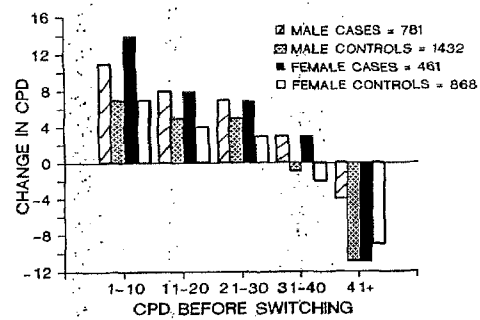
that of controls, i.e. 5.9 versus 3.9 in males and 7.8 versus 4.7 in females. Adjustments for the differences between cases and controls for both duration of nonfilter cigarette smoking and age at switching or age at diagnosis by analysis of covariance did not alter the results.

On the average, both male and female cases had smoked nonfilter cigarettes 1.5–2 years longer than controls (26.3 vs. 24.8 years in males and 22.1 vs. 19.8 years in females). In males, cases and controls smoked filter cigarettes approximately the same length of time (13.5 vs. 13 years) while female cases smoked approximately one year longer than the controls (15.6 vs. 14.3 years).

Figure 1 presents the mean changes in cpd by cpd classes before switching (1–10, 11–20, 21–30, 31–40 and 41+) for males and females. Three points are evident from these results. Most importantly, cases showed greater average compensation than the controls in each cpd class.

FIGURE 1

CHANGES IN CPD ACCORDING TO VARIOUS CATEGORIES OF CPD SMOKED BEFORE SWITCHING



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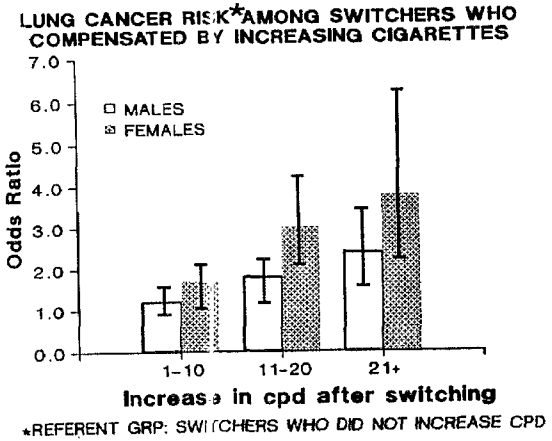
The differences in compensation between cases and controls within classes were statistically significant at $p<0.05$ for all the classes in males and for the first four classes in females. Compensation in cpd was evident only when the initial cpd was less than 30. When initial cpd was greater than 30, there was a tendency either not to increase or even to decrease cpd after switching. In both cases and controls, the extent of compensation progressively declined with increasing cpd before switching. The difference in cpd after adjustments using analysis of covariance for age at switching and duration of nonfilter cigarette smoking did not alter these results appreciably.

Figure 2 shows a clearcut dose-response relationship for lung cancer with increasing levels of changes in cpd (compensation), relative to those who did not increase cpd, after adjusting for duration of nonfilter and filter

FIGURE 2



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cigarette smoking, nonfilter cpd, and age at switch. The odds ratios increased from 1.2 to 2.4 in males and 1.7 to 3.8 in females corresponding with increases of 1-10 to 21+ cpd after switching. The test of linearity was significant at $p<0.05$.

The risk associated with increasing cpd versus decreasing cpd after switching, relative to those who did not change cpd, was also examined. Compared to those who did not change their cpd, those who increased cpd had an odds ratio of 1.38 (1.13-1.69) in males and 2.19 (1.67-2.89) in females. In contrast, males who decreased cpd had a statistically significant reduction in the odds ratio to 0.64 (0.47-0.86), whereas in females, the the number of cases who decreased cpd (n=46) was small and hence the corresponding odds ratio = 0.97 (0.62-1.55) did not show a significant reduction.

Since greater compensation occurred among those who initially smoked <30 cpd (Figure 1), we examined the risks associated with increasing cpd according to those who initially smoked < 30 cpd and >30 cpd. Among those who initially smoked <30 cpd, those who increased cpd had a statistically significant elevation in the odds ratio for lung cancer, relative to those who did not increase cpd, after adjustments for age at switch, duration of nonfilter and filter cigarette smoking (odds ratio = 1.46 ; $p<0.001$ in males and odds ratio = 2.38; $p<0.001$ in females). Among those who initially smoked >30 cpd, the corresponding odds ratio was significantly elevated (odds ratio = 1.73; $p<0.02$) in males only. In females, (odds ratio = 1.5, $p<0.4$) the numbers of cases (n=59) and controls (n=69) were relatively small.

The regression of compensation (filter cpd - nonfilter cpd) on nonfilter cpd yielded negative slopes, indicating that the level of nonfilter cigarette smoking was a negative predictor of compensation i.e. the lower the initial nonfilter cpd, the greater the compensation.

DISCUSSION

The results of this study indicate that a sizeable portion of smokers tend to compensate (increase cpd) after switching from nonfilter to filter cigarettes but more importantly, that patients with lung cancer compensate more

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than controls even after adjustments for confounding covariates such as age at switch or age at diagnosis, and duration of nonfilter cigarette smoking. A greater proportion of females (50–60%) than males (40–45%) showed compensation in cpd.

Among switchers who increased cpd, there was a clearcut dose-response relationship for risk of lung cancer with increase in cpd, relative to those who did not increase cpd after switching. Using switchers who did not increase cpd as the referent group, odds ratios increased from 1.2 to 2.4 in males and 1.7 to 3.8 in females corresponding to increases of 1–10 to 21+ cpd after switching (Figure 2). The linearity of the dose response pattern in both sexes (tests for linear trend were significant at $p<0.05$) support the biological plausibility of compensation as an important risk factor for lung cancer.

In our study, the change in cpd was inversely related to cpd smoked initially (Figure 1) i.e. the lower the initial cpd, the greater the tendency to compensate by increasing cpd. In fact, heavy nonfilter cigarette smokers (>30 cpd) on the average tended to decrease rather than increase cpd after switching to filter cigarettes. There may be several explanations for this finding. It is possible that heavy smokers may compensate by altering their smoking topography since there may be a time limitation in smoking additional cigarettes and/or encumbent symptoms might compel them to smoke less upon switching. Another plausible argument that can be made relates to an upper threshold phenomenon of nicotine dependency. In the already heavy nonfilter cigarette smokers (>30cpd), the amount of filter cigarettes smoked (even when it is less than the initial cpd), after switching may be sufficient to maintain their required nicotine level.

Compensation is undoubtedly a complex phenomenon including changes in puff frequency, duration, rate and interval (Sepkovic et al., 1984). Nevertheless, the relatively simple measure of compensation used in this study (increase in cpd after switching) has proved to be an important risk factor for lung cancer.

Previous reports have shown 25 – 35% reductions in risk for Kreyberg I lung cancer for long-term (>10 years) switchers relative to nonfilter only smokers (0.66 in males and 0.74 in females), without adjustment for increase/decrease in cpd after switching (Wynder and Kabat, in press). In the current study, the odds of lung cancer were found to be increased in switchers who compensated by increasing cpd, relative to those who did not (1.51 in males and 2.21 in females). Extrapolating from both sets of results, we project further risk reductions on the order of 46–50% when switchers do not increase cpd after switching (Table 2).

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TABLE 2

RISK OF LONG-TERM SWITCHERS* VERSUS NONFILTER ONLY SMOKERS FOR KREYBERG 1 LUNG CANCER

	OR**Unadjusted for compensation	OR@ for those who compensate	OR@ for those who do not compensate
MALES	0.66 ($p<0.05$)	0.81	0.54
FEMALES	0.74 (NS)	1.10	0.50

*Greater than 10 years of filter cigarette smoking.
**Wynder and Kabat, in press. Adjusted for cpd, age, inhalation and education using logistic regression analysis.
@Computed hypothetically.

Compensation as a risk factor has not been examined in depth in epidemiological studies comparing the health risk of nonfilter to filter cigarette switchers relative to exclusive nonfilter cigarette smokers. Based on our results, the lung cancer risk among smokers who switch to filter cigarettes would be reduced further if they strive not to increase cpd after switching. Proponents of the idea that switching cigarettes is of some benefit, should also advocate that individuals who continue smoking should avoid compensation after switching.

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BEHAVIORAL IMPACT AND COST ANALYSIS OF A WORKSITE SELF-HELP SMOKING CESSATION PROGRAM

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INTRODUCTION

Self-management smoking cessation methods have been available commercially for a number of years and have been discussed in the literature (Kanfer, 1975; Mahoney and Arnkoff, 1975; Lichtenstein, 1978; Glasgow and Bernstein, 1981). Social support methods and monetary incentives are two additional intervention components commonly cited as being helpful in the cessation and maintenance process (Rosen and Lichtenstein, 1977; Kassaye, 1984; Coppotelli and Orleans, 1985). Additionally, the majority of adult smokers have indicated a desire to quit, having tried to quit in the last year or so, and have expressed interest in using self-help smoking cessation programs (DHEW Publication, 1979; Davis, et al.,1984). Lastly, according to a recent review of the literature the worksite represents a commonly recommended site for efficient delivery of smoking cessation services (Windsor and Bartlett, 1984).

While the three smoking cessation intervention methods noted (self-help manuals, social support and monetary incentive) are widely recommended, few rigorous evaluations of behavioral impact and cost analyses using standardized methods of data collection, biochemical validation, experimental designs, and sufficient sample sizes with adequate statistical power are apparent in the employee health promotion literature (Windsor and Bartlett, 1984; Warner, et al., 1988).

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ENVIRONMENTAL EXPOSURES AND LUNG CANCER RISK AMONG WOMEN IN HARRIS COUNTY, TEXAS, 1977-1980

The Univ. of Texas H.S.C. at Houston Sch. of Public Health PH.D. 1984

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ENVIRONMENTAL EXPOSURES AND LUNG CANCER RISK AMONG WOMEN IN HARRIS COUNTY, TEXAS, 1977 - 1980

by

JANET CRANSTEN IVES, M.Sc.N.

DISSERTATION

Presented to the Faculty of the University of Texas

Health Science Center at Houston

School of Public Health

In Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

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ENVIRONMENTAL EXPOSURES AND LUNG CANCER RISK

AMONG WOMEN IN HARRIS COUNTY, TEXAS, 1977 - 1980

By

JANET CRANSTEN IVES, M.Sc.N.

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Member: Robert J. Hardy, Ph.D.

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'tis a far more healthy thing

to prevent disease than

to try and live

in spite of it.

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ENVIRONMENTAL EXPOSURES AND LUNG CANCER RISK

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Supervising Professor: Patricia A. Buffler, Ph.D.

ABSTRACT

Excessively high, accelerating lung cancer rates among women in Harris County, Texas, prompted this case-comparison study. Objectives were to compare patterns of employment, indirect exposures, and sociodemographic variables of lung cancer cases with comparison subjects (compeers) after standardizing for possible confounders, such as age and cigarette smoking. Lung cancer cases were microscopically confirmed, white, Harris County residents. Compeers, chosen from Medicare records and Texas Department of Public Safety records, were matched on gender, race, age, resident and vital status. Personal interviews were conducted with study subjects or next-of-kin. Industries and occupations were categorized as high risk, based on previous studies.

Almost all cases (95.0%) and 60.0% of compeers smoked cigarettes. The odds ratio for lung cancer and smoking is 13.9. Stopping smoking between ages 30-50 years carries a lower risk than stopping at age 58 or more years. Women's employment in a high risk industry or occupation results in consistently elevated, smoking-adjusted odds ratios.

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Frequency and duration of employment demonstrate a moderate dose-response effect. A temporal association exists with employment in a high risk occupation during 1940-1949.

No increased risk appeared with passive smoking. Husband's employment in a construction industry or a structural occupation significantly increased the smoking-adjusted odds ratios among cases and compeers (O.R.= 2.9, 2.2). Smoking-adjusted odds ratios increased significantly when women had resided with persons employed in cement (O.R. = 3.2) or insulation (O.R.= 5.5) manufacturing, or a high rise construction industry (O.R.= 2.4). A family history of lung cancer resulted in a two-fold increase in smoking-adjusted odds ratios. Vital status of compeers affected the odds ratios.

Work-related exposures appear to increase the risk of lung cancer in women although cigarette smoking has the single highest odds ratio. Indirect exposure ro certain employment also plays a significant role in lung cancer in women. Investigations of specific direct and indirect hazardous exposures in the workplace and home are needed. Cigarette smoking is as hazardous for women as for men. Smoking should be prevented and eliminated.

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CHAPTER ONE

Introduction

The occurrence of cancer is affected by the life style and environment of men and women (WHO, 1964) and, therefore, the investigation and analysis of factors that may contribute to the occurrence of cancer need to be comprehensive:

> Current trends in cancer incidence give no urgent cause for alarm, but many industrial products have been introduced so recently (and on such a large scale...) that even if they do prove hazardous or if they replace a hazard with a less hazardous product, their effects would not yet be apparent. Although we can attribute only a nominal "less than 1%" of all current cancer deaths to such products, we must reiterate our conclusion from some previous sections: There is too much ignorance for complacency to be justified (Doll and Peto, 1981, p. 1251).

Lung cancer rates for women in the United States and Canada have reached epidemic proportions and predictions indicate that lung cancer mortality rates for women will soon resemble rates among men (Burbank, 1972; Mao, 1983; Stolley, 1977, 1983; Vincent et al., 1977). Others predict that the rates for women will be lower than those for men because of the differences in cigarette smoking exposures

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(Schneiderman, 1977; USPHS, 1979; Wynder et al., 1973). The increase in lung cancer mortality among women in various States has been widely documented (American Cancer Society, 1981; Arellano et al., 1972; Austin et al., 1979; Beamis et al., 1975; Devesa and Silverman, 1978, 1980; Meigs, 1977; Rothschild et al., 1979; Stolley, 1977; USPHS, 1981) and projections suggest that lung cancer will soon surpass breast cancer as the leading cause of cancer mortality among women in the United States and Canada (Greenwald & Polan, 1979; Irwin, 1980; Moore, 1980; USPHS, 1981, 1982; CDC, 1982, 1984). In at least two states (Kentucky and Washington), lung cancer mortality rates already have exceeded mortality rates of breast cancer among women (CDC, 1984). Internationally, the United States leads the world in the percentage increase (39%) that occurred in female lung cancer mortality rates between 1965-1969 and 1970-1972 (Benjamin, 1977).

Prior to 1930, lung cancer was reported so infrequently as a cause of death that it was not specifically identified in the mortality statistics of the United States and most other countries of the world (Dorn, 1954). Since the early 1950's, however, lung cancer has been the leading cause of death among men in the United States and rates among women have accelerated rapidly. The mortality rate from lung cancer and other respiratory sites among white women in the United States tripled between 1950-1959 and 1970-1979 (5.1 per 100,000 to 15.3 per 100,000)

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(Table 1).

In Texas, the mortality rate from lung cancer and other respiratory sites rose from 5.2 per 100,000 white women to 15.7 per 100,000 in 1970-1979, while in Harris County the mortality rate from lung cancer among white women increased from 6.0 per 100,000 to 22.4 per 100,000 during these same time periods (Table 1). This represents an increase in lung cancer mortality rates among white women of 272 percent in Harris county. Harris county has the highest rate in all counties in Texas in which at least 50 deaths occurred from lung cancer and other respiratory sites among white women during 1970-1979. Lung cancer mortality rates among white men in Harris County during 1950-1959 were seven times higher than those for women, while during 1970-1979, their rates were less than four times (3.75) times higher. The increase in lung cancer mortality rates among white men in Harris County from 1950-1959 to 1970-1979 was less than half (103 percent) the increase observed for white women during this same period. The increase in rates of respiratory cancer among women in Texas has been reported since the late 1960's (Lee and LaBarthe, 1974; Macdonald et al., 1966).

The majority of lung cancers in women in the United States since 1960 have occurred in women under 65 years of age (Table 2). The rates of lung cancer in this age group are a reflection of the proportional age distribution of women in the population, the exposures or predispositions they may have experienced and acquired throughout their

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TABLE 1

MORTALITY RATES OF CANCER OF THE TRACHEA, BRONCHUS AND LUNG, INCLUDING PLEURA AND OTHER RESPIRATORY SITES 1950-1959,1960-1969, 1970-1979 AMONG WHITE WOMEN AND MEN IN THE UNITED STATES, TEXAS, AND HARRIS COUNTY.

	Mortality rates, per 100,000 during			Percentage Increase*		
Area and gender	1950-1959	1960-1969	1970-1979	60's/50's	70's/60's	70's/50's
United States						
Women	5.1	7.6	15.3	48.0	102.0	199.0
Men	29.6	46.8	64.0	58.0	37.0	116.0
Texas						
Women	5.2	7.9	12.7	53.0	99.0	204.0
Men	27.7	48.6	68.0	76.0	40.0	146.0
Harris County						
Women	6.0	10.6	22.4	77.0	110.0	272.0
Men	41.4	62.9	83.9	52.0	34.0	103.0

Adapted from National Cancer Institute and the Environmental Protection Agency (1983).

*Percentage Increase:
60's/50's = change in mortality rate between 1950-1959 and 1960-1969
70's/60's = change in mortality rate between 1960-1969 and 1970-1979
70's/50's = change in mortality rate between 1950-1959 and 1970-1979

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TABLE 2

PERCENTAGE OF LUNG CANCER DEATHS AMONG WHITE FEMALES WITHIN AGE GROUPS IN THE UNITED STATES, 1950-1977.*

Time period	1950-1954	1955-1959	1960-1964	1965-1969	1970-1974	1975-1977	1950-1977
Age group:							
< 45	7.9	8.3	8.4	7.1	5.3	4.2	6.2
45-54	14.5	15.7	18.3	19.6	18.7	16.4	17.6
55-64	25.5	24.1	24.7	26.9	30.0	30.8	28.0
65-74	30.2	29.4	27.1	25.8	26.0	28.4	27.3
75+	21.9	22.5	21.6	20.6	20.1	20.3	20.8
< 65	47.9	48.1	51.3	53.5	53.9	51.4	51.9
≥ 65	52.1	51.9	48.7	46.5	46.1	48.6	48.1
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

* Adapted from N.C.I. Cancer Mortality in the United States: 1950-1977. Monograph 59, 1982.

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lives, and the length of time it takes for the disease to develop. The annual percentage increase in lung cancer mortality among women in the United States from 1968 to 1978 has been greater in those 65 or more years of age (6.9%) than in women less than 65 years of age (6.3%) (Doll and Peto, 1981). This suggests that lung cancer rates among middle-aged women will stop rising by the turn of the century but rates among older women may continue to rise (Doll and Peto, 1981). Among women 30 to 39 years of age in the United States during 1970 to 1979 (1940 birth cohort), mortality rates from lung cancer seem to have stopped rising recently (Figure 1).

The incidence of lung cancer among white females is higher than that among black females while the mortality has been almost identical for both races since 1955 (Devesa and Silverman, 1978). Hu and White (1979) reported the incidence of lung cancer among black females in Alameda County during 1960 to 1969 to be slightly higher than the incidence among white females. Lower incidence rates of lung cancer in Los Angeles during 1972 to 1976 and in San Francisco during 1969 to 1973 were reported among black females than among white females (Menck and Henderson 1978). Burbank and Fraumeni (1972) reported a lung cancer mortality ratio of 1.04 for black females compared to white females in the United States during 1962 to 1967. An excess of lung cancer mortality during 1960 to 1967 was reported among both black female and white female migrants born in the South compared with lung

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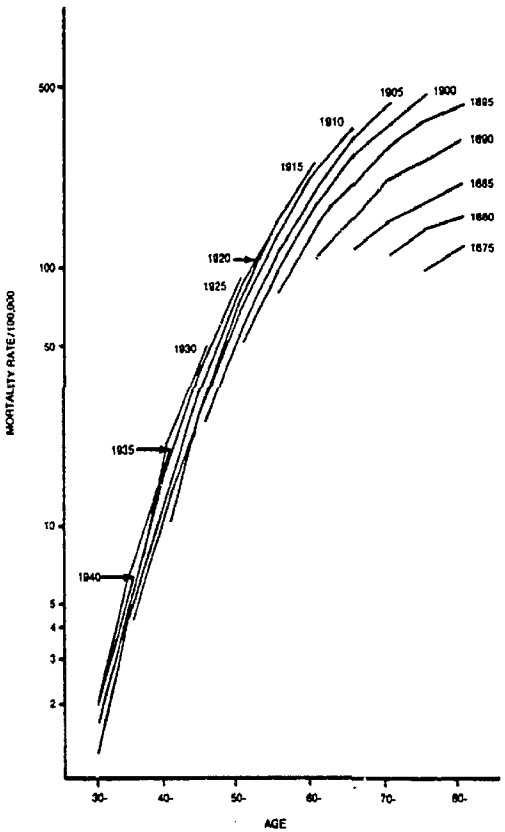

Figure 1. Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death for females, United States, 1950-1975.

Source: National Cancer Institute (1982)

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cancer mortality rates among black females and white females born in Ohio (Mancuso, 1977).

The natural history of lung cancer is incomplete because of the late stage of development at which the majority of tumors are diagnosed. Lung cancers include a wide spectrum of malignant neoplasms that may be endodermal, mesodermal, or possibly neuroectodermal in origin (Matthews and Gordon, 1977) and many are a mixture of cell types. Approximately 90 percent of all lung cancers are of four main histopathologic categories: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma (Galofre et al., 1964; Robbins and Angell, 1971; Selawry and Hansen, 1973). Different theories describing the development of lung cancer have been proposed. Seydel and associates (1975) proposed that during the early development of lung cancer there is a gradual transition from the normal bronchial epithelial lining to squamous metaplasia to carcinoma-in-situ and, finally to locally invasive carcinoma, occurring over a period of five to ten years. Auerbach and coworkers (1979) believe that the pathogenesis of bronchogenic carcinoma is a continuum beginning with a few mildly atypical mucosal cells and, finally, to invasive carcinoma. They also suggest that the progressive mucosal atypia occurs over a period of many years and that carcinoma-in-situ remains as such for several years before the invasion occurs. Furthermore, they believe that at each step the process is potentially reversible.

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Environmental exposures, such as smoking tobacco and employment in hazardous occupations, have been estimated to contribute 77.4% and 5.0%, respectively, to the excess lung cancer occurring among women in the United States (Doll and Peto, 1981). Among men in the United States, the estimates of excess lung cancer due to environmental exposures are higher: smoking tobacco = 90.9%, hazardous occupational exposures = 15.0%. Cigarette smoking became widespread among women born after 1920 (USDHHS, 1981) and the proportion of women in the labor force has increased markedly since the early 1900's. It is possible that the increased consumption of tobacco by women, along with their increased rates of employment, has contributed to the current epidemic of lung cancer. Other factors, such as indirect or secondary exposures to carcinogens, the use of aerosol propellants, and family history of lung cancer have also been considered. Few studies of associations between recognized or potential carcinogens and lung cancer have been conducted among women. Of those studies with an adequate sample size, many have incomplete information on major variables, such as, smoking status and employment histories.

This study compares a group of 537 white women, with or without lung cancer, who provided information on these variables. Information was obtained in a standardized manner during a personal interview with cases and comparison subjects or their next-of-kin. It is hoped their contributions may provide us with a clearer understanding of the risks of lung cancer among women so that prevention may

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be more effectively accomplished.

OBJECTIVES OF THE STUDY

1. To compare patterns of high risk employment, that is, ever employed, frequency of employment, duration of employment, and year of employment, in high risk occupations and high risk industries between women with lung cancer with those of their compeers.
2. To investigate the strength of associations between employment in a high risk occupation or a high risk industry and the subsequent occurrence of lung cancer, after standardizing for recognized risk factors and confounders, such as, cigarette smoking and age, of the lung cancer cases and their compeers.
3. To compare exposures to potentially hazardous substances experienced by cases at home, that is, having lived with person(s) exposed to carcinogenic agents in an occupation or industry, lived with person(s) who smoked cigarettes, use of hair spray or hair dryers, with the experiences of their compeers.
4. To compare demographic and socioeconomic variables, that is, location and duration of residence, highest level of education attained, religious preference, and marital status, and other possible confounding factors among white women with an initial diagnosis of lung cancer with women without lung cancer of similar ethnic and age

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characteristics.

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CHAPTER TWO

Literature Review

One of the earliest epidemiologic studies of lung cancer remains the most significant study of lung cancer among women to date in that a clear association was established in this investigation between cigarette smoking and lung cancer in both women and men (Doll and Hill, 1952). Since then, findings from at least 25 retrospective studies and eight prospective studies, mostly conducted in the United States, have supported this association (USPHS, 1982). Smoking has been the chief and frequently the only risk factor examined in studies of lung cancer in women. Basic demographic and socio-economic factors, such as residence, occupation, education, and marital status usually have not been reported. Selected studies of lung cancer in women published since 1950 are examined in Appendix A, Table 1.

Studies of lung cancer in women in the past have relied heavily on medical or hospital records and mailed questionnaires as the primary source of information (Appendix A, Table 1). Epidemiologic studies which depend chiefly on medical records, death certificates, or

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questionnaires are often limited by incomplete entries of pertinent data (Demlo et al., 1978; Glasser, 1981; Percy et al., 1981). The accuracy of occupation and industry data on death certificates for white males has recently been reported as 73.5% for occupation and 72.1% for industry (Steenland and Beaumont, 1984). In the single study of women's employment considered by the same authors, the accuracy of data on death certificates for occupation was 45.3% and for industry it was 60.4%. Personal interview schedules are generally designed specifically for a particular study and tend to elicit more complete information on the variables of interest. It is important that the interview schedule be standardized and applied in a similar manner to all study subjects. Some early studies of lung cancer in women were compromised by cases residing in or receiving therapy in diverse geographic areas and data were collected by interviewers with different levels or expertise of interviewing skills (Haenszel et al., 1958; Haenszel and Taeuber, 1964; Hammond, 1966; Wynder and Graham, 1950; Wynder et al., 1956). Seven of the 21 reports of lung cancer case series in women had no comparison groups (Beamis et al., 1975; Cooper et al., 1968; Deaner and Trummer, 1970; Hanbury, 1964; Hammond, 1966; Lombard and Huyck, 1968; Kennedy, 1973). In the studies which included comparison subjects, matching comparison subjects with cases on important variables, such as age, was not frequently included in the study design.

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Smoking

Risk ratios of lung cancer mortality for smokers compared with nonsmokers in studies among women in the United States conducted since 1950 range from 1.4 to 6.78 and, among men the range in risk ratos for smokers is higher: 1.5 to 13.0* (USPHS, 1982). The percentage of excess lung cancer deaths attributed to tobacco smoking among women in the United States in 1978 (77.4%) is predicted to increase as lung cancer deaths occur among older women who have smoked more cigarettes for longer periods of time (Doll and Peto, 1981).

A comparison of the prevalence of cigarette smoking among birth cohorts (Figure 2) with the lung cancer mortality experience among birth cohorts (Figure 1), shows a strong relationship between cigarette smoking behavior and lung cancer mortality (USPHS, 1982). The highest prevalence of cigarette smoking (44 percent) is observed for the birth cohorts of 1921-30 and 1931-40 in 1960; women who would be between ages 40-59 years in 1980. This cohort is approaching the age where the absolute excess of deaths of smokers over nonsmokers are expected to become substantial (USPHS, 1981). The cohort born during 1911 to 1920 have experienced lower rates of smoking than susequent cohorts; however, their duration of smoking has been longer and use of filter-tip cigarettes has been less than that of cohorts born later.

* Studies included at least 5 cases who were nonsmokers.

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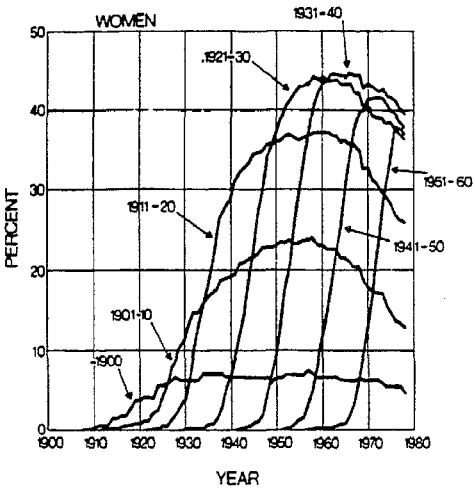

Figure 2. Changes in the prevalence of cigarette smoking among successive birth cohorts of women, 1900 - 1978.

Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S.National Center for Health Statistics.

Source: USPHS (1981).

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This cohort, born during 1911 to 1920, attained an age in 1980 (60 to 69 years of age) where the absolute number of excess lung cancer deaths of smokers over nonsmokers occurs. When lung cancer mortality rates are examined by birth cohorts, cohorts with increasing smoking prevalence also have increasing age-specific rates of lung cancer. The shift toward the left by each succeeding birth cohort in the age-specific graph of lung cancer mortality rates indicates that rates are rising among increasingly younger age groups (USPHS, 1982).

The observed increase in smoking among women occurred before and after World War II which is about 20 or 30 years later than the increase in smoking among men (USPHS, 1979). World War II drew many women into the work force to fill jobs left vacant by men and, late in the war, the labor force participation rate of women 16 years of age or more reached 37 percent (Waite, 1981). It is possible that the simultaneous occurrence of these two factors, increased rates of smoking and increased participation by women in the labor force, may have produced greater risks of disease among women.

Patterns of smoking among workers in various industries and occupations have not been well documented. Sterling and Weinkam (1976, 1978) reviewed smoking patterns by major occupation based on the 1970 National Health Interview Survey. They found the prevalence of smoking among women was similar to the prevalence among males in many

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different occupations. Smoking was more prevalent among employed women than among women not employed or among women employed in traditional types of women's work such as housewife. Estimates from the National Health Interview Survey reveal that, in 1976, the percentage of women of all ages who reported smoking on a regular basis ranged from 29.0% to 56.3% across various occupational categories (Table 3). Occupations with the highest percentages of reported smoking among women were: Laborers (56.3%), Managers and Administrators (41.6%), Craftsmen and Kindred Workers (40.5%), and Service Occupations (39.0%). These distributions of smoking rates were higher than those reported by men for Laborers, and Managers and Administrators. Homemaking had the lowest reported rate of smoking among women (29.0%). However, 37.1% of Homemakers 20 to 44 years of age were smokers.

Patterns of smoking vary not only among occupational groups but between ethnic groups as well. Holck et al. (1982) reported in a survey of 51 counties on the United States side of the U.S.-Mexico border in 1979, that the rate of smoking among white females (31.6%) is higher than the rate among Mexican-American women (18.5%). Survey data on adolescent smoking habits in 1979 reveal that by ages 17 to 18 years, rates of smoking among women (26.2%) exceed that among men (19.3%) (USPHS, 1981).

The proportion of smokers among women with lung cancer reported in studies conducted in the United States and Europe ranged from 32.3% to 91.2% (Appendix A, Table 2).

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TABLE 3

ESTIMATES OF THE PERCENTAGE OF CURRENT, REGULAR CIGARETTE SMOKERS, ADULTS AGES 20 YEARS AND OVER, ACCORDING TO LABOR FORCE STATUS AND OCCUPATION AND SEX, U.S., 1976

	Female			Male		
	Total 20+	20–44	45–64	Total 20+	20–44	45–64
Total	32.0	36.9	34.8	41.9	47.6	41.3
Currently employed	35.9	37.0	36.1	43.4	46.8	39.7
White collar total	34.3	33.8	36.9	36.6	38.6	35.3
Professional technical and kindred	29.1	28.6	32.7	30.0	31.1	29.9
Managers & administrators except farm	41.6	42.7	40.8	41.0	46.4	36.1
Sales workers	38.1	37.0	42.6	39.9	42.6	38.0
Clerical & kindred workers	34.8	34.7	36.0	40.4	40.1	44.2
Blue collar total	39.0	43.7	33.6	50.4	54.1	44.3
Craftsmen & kindred workers	40.5	46.9	35.6	48.0	52.1	41.6
Operatives and kindred workers	37.6	42.5	31.2	52.3	55.3	46.2
Laborer, except farm	56.3	52.6	*	53.7	56.9	51.7
Service	39.0	42.8	37.2	47.2	51.1	44.8
Farm	32.2	51.0	*	36.9	45.4	35.0
Unemployed	40.0	41.0	39.2	56.8	59.9	53.8
Usual activity— homemaking	29.0	37.1	32.2	NA	NA	NA

NOTE: Unknown if ever smoked excluded from calculation.
*Figure does not meet standards of reliability or precision.

Source: USDHHS (1981)

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international studies among populations primarily of Oriental origin report lower proportions of smokers among women with lung cancer (22.5% to 77.6%). If only those studies in which information was obtained by interview with cases in the United States and Europe are considered and all smoking histories are known, the proportion of smokers reported among women with lung cancer ranges from 63.0% to 84.2% (Doll, 1952; Wynder, 1973). The wide variability in the proportion of smokers reported in studies of women with lung cancer may be attributed to numerous factors, such as collection of data from medical records (Ashley, 1969; Beamis, 1975; Deaner, 1970; Hinds,1981; Kennedy, 1973; Murakami, 1975; Vincent, 1965), data from physicians, friends, or relatives (Haenszel, 1964; Lombard, 1968; Vincent, 1965), or data from mailed questionnaires (Hammond, 1966). In studies of women with lung cancer, smoking habits were unknown for about one-third of the cases studied (Ashley, 1969; Beamis, 1975; Hinds, 1981; Kennedy, 1973; Murakami, 1975; Vincent, 1977).

The possible health consequences of "passive" smoking have recently received attention (Garfinkle, 1981; Heller, 1983; Hirayama, 1981; Repace, 1984; Stellman and Stellman, 1981; Trichopolous et al., 1981; USPHS, 1982). A recent review of the effects of exposure to other persons' cigarette smoke noted that the findings of three studies (Correa et al., 1983; Hirayama, 1981; Trichopolous, 1981; Garfinkel, 1981) are consistent with an attributable risk of

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30 percent (Weiss et al., 1983). Conclusions of the epidemiologic studies on involuntary or passive smoking are conflicting and further inquiry is needed.

Employment

Comparatively little systematic research has been devoted to examining health hazards to which women may be exposed at work (Stellman, 1978). There are at least 10 major industrial processes and industries, as well as chemicals and groups of chemicals in which there is a causal association between exposure and human lung cancer (see references accompanying Tables 3 and 4 in Appendix B). Data currently available do not permit any precise estimate of the extent of risk, but the number of women employed in six manufacturing industries where the potential for exposure to known or suspected carcinogens exists suggests that a considerable number of women may be in such settings (Table 4).

The rate of employment of white women in the U.S. has more than tripled since 1890 and more than doubled since 1940 (1890: 15.8%; 1940: 24.5%; 1980: 51.3%) (Waite, 1981). The number of women aged 16 years and over employed in the labor force in the United States in 1980 totalled 44.6 million (Waite, 1981). This represented 51.6% of all women of working age in 1980 which is a threefold increase over the percentage of women age 10 years or more who were employed in the labor force during 1890 (17.3%). World War

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TABLE 4

EMPLOYMENT IN MANUFACTURING INDUSTRIES WITH RELATIVELY HIGH EXPOSURE TO KNOWN OR SUSPECTED CARCINOGENS, UNITED STATES, 1972

Industry	Examples of Carcinogens Used	Number Employed (Thousands)	
		Women	Men
Instruments and related products	Asbestos, thallium oxide	170	293
Petroleum and petroleum products	Benzene, polycyclic aromatics	17	172
Leather and leather products	Chrome salts, benzene	180	123
Ordnance and accessories	Asbestos, benzene	42	156
Transportation equipment	Vinyl chloride, benzene	194	1624
Fabricated metal products	Chromates, lube and cutting oil mists	261	1151
		873	3519

Source: Waldron (1980)

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II, and the economic boom which followed, caused a two-peaked lifetime employment pattern for women (Figure 3). Women born during 1916 to 1925 had high employment rates when they were 20 to 24 years of age, a decrease in rate of employment during their childbearing and childrearing ages of 25 to 44, and had reentered the work force in their middle forties and fifties. Women born during 1926 to 1935 show a similar pattern of employment but with higher rates of employment and a smaller decrease in employment at ages 25 to 34 years. Women born during 1936 to 1945 have been more likely to work at all ages than those born earlier and women born during 1946 to 1955 show very high rates of employment which continue through their prime childbearing years. It seems likely that young women in the coming decades will show a new pattern of employment with little decrease in labor force participation during early marriage and motherhood. Projections of composition of the labor force indicate that the number of women employed will range from 57 to 64 million in 1995 (57.9% to 65.2% of women 16 or more years of age) (Fullerton, 1980).

Patterns of employment of women in Texas reflect changes that began to occur nationally in 1950. The proportion of women employed in clerical occupations in Texas in 1940 was 6.9%, increased to 26.9% of women employed in clerical occupations in 1950, and continued to rise until 1970 (32.9%) (Table 5). Occupations in which the percentage of women employed decreased during 1940-70 were: salesworkers, private household workers, and farm laborers.

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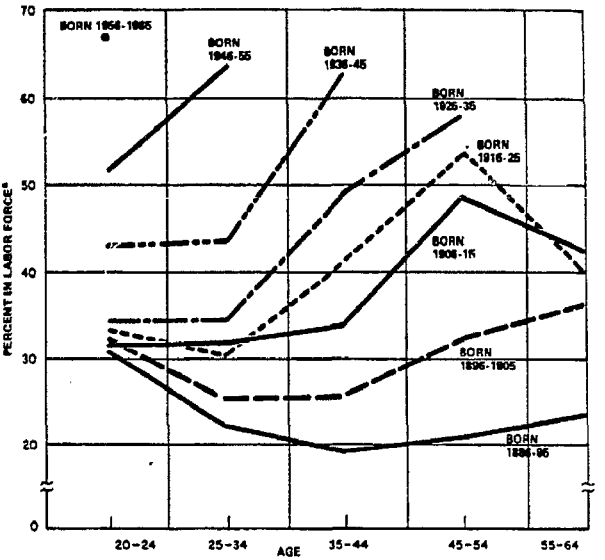

[a]Number in labor force as percent of total noninstitutional population in group specified

Note: For women born between 1886 and 1915, the first age plotted is 14-24 years. Each group (birth cohort) reaches each age interval according to the midpoint of their birth years. Thus, the cohort born 1886-95 reached 25-34 in 1920 and ages 55-64 in 1950. The cohort born 1916-25 reached ages 25-34 in 1950 and ages 45-54 in 1970.

Figure 3. Labor force participation over working life of U.S. women born in selected time intervals: 1886-1965.

Source: Waite (1981)

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TABLE 5

PERCENTAGE OF TOTAL POPULATION EMPLOYED IN TEXAS IN MAJOR OCCUPATIONS IN 1940, 1960, and 1970 WHO WERE WOMEN

Occcupation	1940	1950	1960	1970
Private household workers	27.0	13.1	11.4	5.1
Sales workers	15.4	9.9	8.4	7.5
Service workers, except private household	13.0	15.0	15.4	16.4
Professional, technical and kindred workers	12.5	12.2	13.1	14.8
Operatives and kindred workers	8.6	10.4	8.7	8.9
Clerical and kindred workers	6.9	26.0	28.6	32.9
Farm laborers	5.7	3.3	1.4	0.1
Managers, officials, and proprietors, except farm	4.6	5.5	4.9	4.0
Farmers and farm managers	2.2	1.0	0.6	0.2
Craftsmen, foremen, and kindred workers	0.6	1.2	1.1	1.7
Laborers	0.5	0.6	0.8	0.9

Sources: 1940 Census of the Population, Vol.III, The Labor Force;
1950 Census of the Population, Vol.II, Characteristics of the Population, Part I; 1960 and 1970 Census of the Population,Texas, General Social and Economic Characteristics.

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Patterns of employment of women in Harris County were similar to those of Texas with a marked shift from employment as Domestic Service Workers (30.7%) in 1940 into other types of employment in 1950 (Table 6). The employment of women during 1940 to 1950 in Harris County into less traditional occupations such as Professional and Semi-professional Workers, Operatives and Kindred Workers, Proprietors, Managers and Officials, except farm, and Craftsmen, Foremen, and Kindred Workers, increased 4.5 percent (Table 6).

The increase in the employment of women in non-traditional occupations paralleled the influx of larger proportions of women into the labor market during and following World War II (Anderson, 1942; Baetjer, 1946; Bradbury and Evans, 1943; Leach, 1945; Mettert, 1942; USBLS, 1942; USDL, 1942). Some of the important changes in industry which occurred during this period were: increased use of cutting oils, increase in grinding occupations, replacement of shot blasting with sand blasting, use of more concentrated solutions in pickling, wider use of solvents, more frequent use of X-rays, expanded use of welding, and longer working hours (Mettert, 1942). Some of the occupations in which women were employed included making ammunitions, aircraft, aircraft parts, electrical machinery; detail assemblers, filling drums with alcohol or lacquer, machine operation (drill presses and lathes) and assembly, machine shop inspectors, oilers, preparation of

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TABLE 6

PERCENTAGE DISTRIBUTION OF THE FEMALE LABOR FORCE IN MAJOR OCCUPATIONS IN HARRIS COUNTY, TX, IN 1940, 1950, 1960, AND, 1970

Occupation	1940	1950	1960	1970
Domestic service workers	30.7	14.6	12.2	5.4
Clerical, sales, & kindred workers	29.7	41.3	45.0	48.3
Service workers, except domestic	15.4	15.2	15.5	17.2
Professional and semi-professional workers	10.4	11.8	14.1	16.3
Operatives & kindred workers	8.5	9.3	6.9	6.1
Proprieters, managers, & office, except farm	3.8	5.4	4.5*	3.9
Craftsmen, foremen, & kindred workers	0.7	1.4	1.1	1.6
Laborers, except farm & mine	0.7	0.6	0.5	1.0
Farm laborers & foremen	-	0.2	0.1	0.2

* Includes farm.

Sources: 1940 Census of the Population, Vol.III, The Labor Force;
1950 Census of the population, Vol.II,Part I
1960 and 1970 Census of the Population, Texas,General Social & economic characteristics

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intermediates in the synthesis of chematherapeutic agents, testing rubber samples for reaction from antioxidants, and welding (Anderson, 1942; Moushley, 1943; Whipp, 1942). Special publications were issued by the U.S. Employment Service listing occupations suitable for women in war industries (Baetjer, 1942; Anderson, 1942). Designations such as "Rosie the Riveter" highlighted this movement and there were numerous speculations on the health effects on women of employment in high risk areas (Bradbury and Evans, 1943; Kronenberg and Morse, 1943; Varney, 1944). Recently, Blot and Fraumeni (1982) proposed that industrial exposures, such as exposures to asbestos in shipyards during World War II, may account for a substantial part of shifting patterns of lung cancer.

Although women may have experienced different patterns of employment during and immediately following World War II, their distribution throughout occupational categories has changed little since the beginning of the century (USPHS, 1981; Waite, 1981). Women predominate in low-paying, nonunionized occupations. Both of these factors may be associated with increased health and safety hazards (Moore, 1980). A large proportion of employed women work in occupations which appear not to entail serious physical, chemical, or biological hazards: over one-third of women employed in the United States work in clerical occupations, and an additional 14% work as salespersons or teachers. Even these apparently safe occupations, however, may be associated with significant hazards. For example, clerical

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workers may be exposed to hazardous levels of ozone, methanol, or other chemicals from copying and duplicating machines (Moore, 1980).

Less than half of the studies of lung cancer in women published since 1950 considered employment in an occupation or industry as a risk factor in the development of the disease (Appendix A, Table 1). The studies which included occupations used broad groupings of occupations in analysis: in home, outside the home (Beamis et al., 1975); white collar, blue collar, factory, domestic (Haenszel et al., 1958; Wynder et al., 1956); beauticians, non-beauticians (Garfinkel et al., 1977), which restricts identification of specific occupations that may be associated with an increased risk of disease. In some instances, investigators reported that no significant association was noted but the occupations studied were not described (Doll and Hill, 1952; Hanbury, 1964). An analysis of hospital records in Los Angeles County, 1972-75, revealed a significantly increased risk of lung cancer, using proportional and standard incidence ratios estimates (PIR,SIR), among women in three occupations: beautician, assembler, and waitress. (Menck et al., 1977). Information on smoking, however, was not available and reporting of lifetime employment was lacking. The limited examination of occupations in these studies of lung cancer in women may be a reflection of a limited awareness of potential hazards at work for both men and women, recognition of a long latency period for the

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disease, the low proportion of women employed prior to 1950, as well as the perception that women's occupations were not hazardous.

Williams et al.(1977) reviewed the strengths and weaknesses of four large data sources previously used to investigate occupational associations with cancer. The weaknesses identified in these four data sources were: three studies relied on death certificates both for job classification and cancer type (The Registrar General's Decennial Supplement, 1961; Gurainick, 1963; and Milham, 1976); the U.S. Public Health Service and Social Security Administration Study (1967) classified all cancers into only six broad categories; the three U.S. studies were of males only; and the Registrar General's study classified only the occupations for single women. Williams et al. noted that none of these five studies reported data on consumption of tobacco or alcohol and that socioeconomic information was available only in the Registrar General's study.

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Risk estimates of occupations and industries calculated from the Third National Cancer Survey indicated a positive association between lung cancer in women and employment in three industries: Entertainment and Personal Services; Food and Kindred Products; and Wholesale Trade; and one occupational category: Writers, Artists, Entertainers. The major weaknesses of the TNCS study, as indicated by the authors, were the high nonresponse rate for interviews of patients (47% for persons with lung cancer), the absence of important industries other than those located

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

in the survey area (for example, manufacture of wood products, nonferrous smelting and refining, and the petroleum, rubber, chemical, and plastics industries), and the small numbers of patients who had both specific cancers and specific types of employment.

Other Factors

Although cigarette smokers and certain industrial workers are the major groups prone to develop lung cancer, additional factors and the multifactorial aspects of disease causation should also be considered. Some of the major factors requiring study are: differences in rates of lung cancer between men and women, familial and genetic aspects, and socioeconomic characteristics, such as, residence, education, religion, marital status.

Differences in rates of lung cancer between men and women. An extensive literature review of international male to female ratios of lung cancer from 1871 to 1957, with ranges reported between 0.7:1 to 20.9:1, was completed by Kirchoff and Rigdon (1959). A later review of international sex ratios of lung cancer attributes variations among countries to be due primarily to differences in male rates, with female rates being relatively constant (Belcher, 1971). Belcher (1971) suggests there is a genetic influence in the etiology of lung cancer and that the world may be divided into two groups: (1) Europeans and people elsewhere in the

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world of predominantly European origin and, (2) non-European people. Higginson and Jensen (1975) believe that differences in lung cancer incidence rates in females and males are consistent with available information on cigarette smoking habits and neither racial nor migrant studies indicate that genetic factors play an important role in the etiology of lung cancer. Benjamin (1977), reviewing international variations, proposed that the differences in the sex ratios of lung cancer in less-developed countries may be mostly biological due to the "well known additional susceptibility of the male to chest diseases" attributed to the larger size of the male lung which is more likely to collect more bacteria and viruses. He associated higher industrialization in developed countries with the higher mortality rates of lung cancer in men. Lilienfeld (1980) proposed that, in order to interpret differences in cancer mortality between the sexes, three hypotheses may be entertained. One hypothesis states that the differences result from increased exposure of the male to exogenous factors (environmental hypothesis). Another hypothesis states that the differences are explained by an increased predisposition of males , with exposure remaining the same for both sexes (endogenous or constitutional hypothesis). The third possibility is that both factors may be involved and that the cancer results from the interaction of the two factors. Lilienfeld also noted that cancer sites observed more frequently among males are those in the upper end of the gastrointestinal and

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respiratory tracts, that is, parts of the body which are heavily exposed to the external environment. Steroidal differences between women and men have been suggested as partly accounting for differences in liability for lung cancer (Kotin, 1968). About half the difference in life expectancy between women and men has been attributed to differences in smoking (Holden, 1983).

Familial and genetic aspects of lung cancer. The relevance of genetic susceptibility to lung cancer is obscure (Doll and Peto, 1981). Some genetic hypotheses to decribe the influence of environmental agents, such as cigarette smoking, have been outlined by Tokuhata (1972). Two of the early studies of lung cancer in women (Hanbury, 1964; Lombard and Huyck, 1968) found nothing of significance in a review of family histories. Both of these studies were limited by the collection of information from medical records. Others have proposed that women who develop lung cancer are more extreme with respect to genotype than are men who develop lung cancer (Fain et al., 1981). A twofold to threefold excess in the frequency of the specific types of cancer among relatives has been recognized (Clemmesen, 1965; Anderson, 1974; Lilienfeld, 1980) and a specific tendency for lung cancer to aggregate in families has been reported (Tokuhata and Lilienfeld, 1963).

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Demographic and Socioeconomic Aspects of Lung Cancer. Demographic and socioeconomic variables, such as

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residence, education, and marital status have been reported in about one-third of the studies of lung cancer in women (Appendix A, Table 1) and, generally, no "striking effect" or statistical differences were reported for these variables. However, in those studies which examined the demographic or socioeconomic aspects, most of the data sources used are generally limited in information on these variables. Haenszel and Taeuber (1964) found that risks among urban residents and mobile populations with three or more exposure residences were higher than rural and stable populations. They also showed that excess risks for farm-born women migrating to metropolitan counties persisted among both nonregular and regular smokers. Goldsmith (1980) in examining studies by Haenszel et al.(1962); Haenszel and Taeuber (1964); and Hammond (1972), suggested that analysis of the contribution of smoking to the "urban factor" requires further consideration and that a more serious effort should be taken to examine occupational mortality. Standardization for socioeconomic class explained about 88% of the total variation in cancer mortality in 25 major occupational categories in England and Wales, 1970-72. (Fox and Adelstein, 1978). Considering this, Doll and Peto (1981) have warned against incautious interpretation of differences in the risks of lung cancer seen in different occupations. Investigators in two recent case-comparison studies, one conducted in Singapore (MacLennan et al., 1977) and another conducted in Hawaii (Hinds et al., 1981) concluded that cigarette smoking is not the only , nor even the major,

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cause of lung cancer in women and speculated that socioeconomic factors may be important risk variables. Devesa and Diamond (1983) reported strong significant inverse trends between lung cancer incidence and both income and education among white males and black males but no strong trends in risk with income or education were observed for lung cancer among females of either race.

Housewives (married only) in the United States spend an average of 23 hours per day indoors (Moschandreas,1981). The importance of the quality of indoor air is becoming of increasing concern and Hinkle and Murray (1981) cite several studies that suggest a variety of substances, such as, cooking and heating appliances, "household products", asbestos, radon, and formaldehye, that are potentially hazardous to the health of household residents. The use of self-pressurized products containing vinyl chloride monomer such as aerosol hair spray, was banned by the U.S.Consumer Products Safety Commission in 1974 following recognition that concentrations as high as 1000 milligrams per cubic millimeter (400 parts per million) could persist for several hours after spraying in enclosed spaces (IARC, 1974). An association of lung disease with excessive hair-spray use was reported as early as the 1960's (McLaughlin, 1963; Bernstein, 1972; Palmer et al., 1979; Wright, 1981) but this association has been questioned by others (Brunner et al., 1963). A significant annual excess of lung cancer mortality among housewives (17.3 per 100,000) compared with

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employed women (10.8 per 100,00) but smoking patterns were not described (Morton, 1981).

The effects of indirect or "bystander" exposures have been extensively reported, particularly in relation to activities involving asbestos (Anderson et al., 1976, 1979; Daum et al., 1977; Epler et al., 1979; Lilis et al., 1975, 1976, 1979; McGinty, 1975; Newhouse and Thompson, 1965; Selikoff, 1977; Vianna et al., 1978). Parenchymal and/or pleural radiographic abnormalites were found among 48.0% of the wives of asbestos workers following a mean exposure of 2.2 years, (Anderson et al., 1979). Among residents in the home of workers employed in asbestos related industries, a risk factor of 10 was estimated for mesothelioma (Vianna and Polan, 1978).

In summary, studies of lung cancer in women have been seriously limited in the type and quality of information obtained. Medical or hospital records have been the main source of information in many studies; lifetime employment histories were seldom obtained and, in those studies that did report usual or recent occupational histories, broad occupational classifications were used. Not all studies included concurrent comparison groups and, of those that did, the groups selected were often not appropriately comaparable, such as comparisons with males. Information on smoking patterns was often missing in studies that considered womens' occupations and most studies did not consider basic demographic and socio-economic variables. More comprehensive studies of lung cancer in women that

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include information for all home and work exposures of possible importance are needed.

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CHAPTER THREE

Study Methods

This study is part of a lung cancer and larynx cancer project conducted in six counties in the Texas Gulf Coast Area (TGCA) by the University of Texas School of Public Health (UTSPH) in collaboration with The National Cancer Institute (NCI). The TGCA is a highly industrialized and rapidly growing urban-rural area surrounding the city of Houston, the 4th largest city in the United States and the county seat of Harris County. The population of Harris County increased 38.3% from 1970 (1,741,912) to 1980 (2,409,544) (Houston Chamber of Commerce, 1981). Harris County is located in an area rich in oil, gas, and sulfur and Houston ranks first in the nation as a petrochemical refinery center and in the manufacture of agricultural chemicals, fertilizers, and pesticides. Houston has more than 2,743 various manufacturing plants and the manufacture of petrochemicals and agricultural products has been present in the Houston area since the 1940's.

Harris County was selected as a study area because of the excessively high and increasing rates of lung cancer among women in the county, and the large number of women

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with lung cancer who may have had exposure(s) to harmful substances in work areas in a highly industrialized geographic area. Also, it was expected that a substantial number of women with lung cancer may not have smoked cigarettes, thus permitting an examination of risk factors other than smoking.

All cases of cancer of the lung, trachea , or bronchus newly diagnosed on 1 July 1977 through 30 June 1980 in white women 30 to 79 years of age were identified through the Statewide Cancer Reporting System (SCRP), and local hospital discharge lists. The majority (80%) of the 49 hospitals in Harris County participated in the study and they varied in size from less than 100 beds (8), 100-299 beds (17), 300-499 beds (8), to 500 or more beds (6). The size of the 10 hospitals which refused to participate in the study varied from less than 100 beds (1), 100-299 beds (6), to 300-499 beds (3).

Criteria for cases to be included in this study were:

1. a diagnosis of lung cancer coded , either on the patient's medical record or in the records of the SCRP, with one of the following International Classification of Disease Adapted(1979)(ICDA code): Malignant neoplasm of the larynx (161), Malignant neoplasm of the trachea, bronchus, and lung (162), Neoplasm of unspecified nature of respiratory organs, larynx (231.1), Neoplasm of unspecified nature of respiratory organs, lung (231.2);

2. microscopic confirmation of a lung cancer diagnosis either on a pathology report in the patient's medical record or from records in the SCRP;

3. a most recent residence of 1 year or more in Harris County.

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A total of 389 cases were eligible for interview after those with a Spanish-surname, identified by a computer program (Buechley, 1961) and by response to a question on ethnicity in the personal interview, had been excluded from the study. The physicians of 10 of these eligible cases refused permission for interview (Table 7). A total of 43 eligible case-respondents refused to be interviewed and 65 additional cases could not be located, lived outside the study area, or study procedures were not followed correctly by the staff. The number of cases interviewed totalled 271 and, from this group, 12 cases were excluded because criteria for this study were not met. The number of eligible cases included in the study and analysis is 259.

Both living and decedent comparison subjects (compeers) were selected and matched with cases on the basis of gender, race, vital status at time of ascertainment of cases, and county of residence. Group-matching was done in 5-year age groups and, for 87.3% of the cases and compeers there was a difference of less than 1 year in dates of birth. No age-match exceeded 4 years difference in birthdates. Compeers for living cases born between 1901 and 1911 were chosen randomly from Medicare records provided by the Health Care Financing Administration (HCFA) and compeers were selected randomly from the records of the Texas Department of Public Safety for living cases born between 1912 and 1950. Compeers for decedent cases were chosen from computer tapes of mortality, 1976 to 1980,

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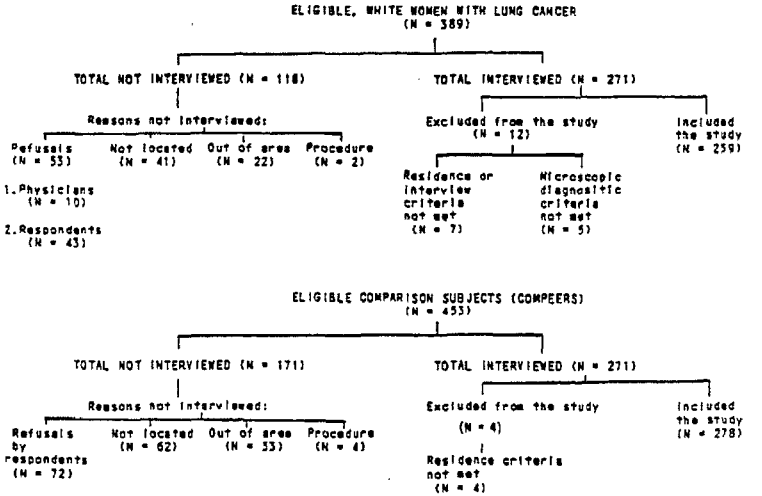
TABLE 7

REASONS INTERVIEWS WERE NOT COMPLETED WITH CASES AND COMPEERS BY VITAL STATUS


ELIGIBLE, WHITE WOMEN WITH LUNG CANCER
(N = 389)
TOTAL NOT INTERVIEWED (N = 118)
TOTAL INTERVIEWED (N = 271)
Reasons not interviewed:
Refusals (N = 53)
Not located (N = 41)
Out of area (N = 22)
Procedure (N = 2)
1. Physicians (N = 10)
2. Respondents (N = 43)
Excluded from the study (N = 12)
Included the study (N = 259)
Residence or interview criteria not met (N = 7)
Microscopic diagnostic criteria not met (N = 5)
ELIGIBLE COMPARISON SUBJECTS (COMPEERS)
(N = 453)
TOTAL NOT INTERVIEWED (N = 171)
TOTAL INTERVIEWED (N = 271)
Reasons not interviewed:
Refusals by respondents (N = 72)
Not located (N = 62)
Out of area (N = 33)
Procedure (N = 4)
Excluded from the study (N = 4)
Included the study (N = 278)
Residence criteria not met (N = 4)

	CASES						COMPEERS					
	All		Living		Deceased		All		Living		Deceased	
Interviews	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Number eligible	389	100.0	85	100.0	304	100.0	453	100.0	123	100.0	330	100.0
Interviewed	271	69.7	45	52.9	226	74.3	282	62.3	78	63.4	204	61.8
Not interviewed:	118	30.3	40	47.1	78	25.7	171	37.7	45	36.6	126	38.2
Refusals	53	13.6	23	27.1	30	9.9	72	15.9	29	23.6	43	13.0
Physician	10	2.6	10	11.8								
Respondent	43	11.1	13	15.3	30	9.9	72	15.9	29	23.6	43	13.0
Other	65	16.7	17	20.0	48	15.8	99	21.9	16	13.0	83	25.2
Not located	41	10.5	10	11.8	31	10.2	62	13.7	9	7.3	53	16.1
Outside study area	22	5.7	7	8.2	15	4.9	33	7.3	7	5.7	26	7.9
Incorrect procedure	2	.5			2	.7	4	.9			4	1.2

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provided by the Texas Department of Health, Bureau of Vital Statistics. Compeers with a history of respiratory cancer, chronic respiratory disease, or a respiratory disease associated with exposure to a specific substance were excluded from the study (see Appendix B, Table 1 for list of excludable diseases). The death certificates of decedent compeers whose next-of-kin reported them as having had one or more of the excludable diseases, such as lung cancer, were reviewed. Compeers whose underlying cause of death on the death certificate was attributed to an excludable disease were removed from the study. Potential compeers whose cause of death was homicide or suicide were also excluded for humanitarian reasons. A total of 453 compeers were eligible for inclusion in the study. The number of compeer-respondents who refused to be interviewed was 72 and 99 additional compeers could not be located, lived outside the study area, or study procedures had not been correctly followed. Four compeers were excluded from the study because residence criteria were not met, leaving a total of 278 compeers who were included in the study and analysis.

Data collection

Abstracts of medical records. The medical records in hospitals where cases had been admitted for diagnosis or treatment were abstracted to obtain pathologic confirmation of the diagnosis of lung cancer and to collect demographic information. Two groups of abstractors were employed:

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experienced abstractors from the SCRP and staff from the Epidemiology Research Unit of the University of Texas School of Public Health (UTSPH-ERU) who were trained by the SCRP staff. A modified, longer version of the SCRP abstract form was used by the UTSPH-ERU staff (Appendix B, Forms 1 and 2).

A sample of abstracts, including 80 cases of lung cancer and 20 cases of larynx cancer, were reabstracted. These abstracts were selected to constitute approximately 5% of all abstracts completed by the SCRP staff and 5% completed by the UTSPH-ERU staff in Harris County hospitals. The quality of the abstracted data in the sample of cases with comparative information available appeared quite good. A complete description of the reabstracting results may be found elsewhere (Buffler et al., 1983).

Medical abstracts of all eligible cases who were interviewed were rechecked and verified for a microscopic diagnosis of lung cancer. Abstracts were unavailable for 24 cases whose information was initially obtained from a computer tape either from the SCRP (19 cases) or the University of Texas Medical Branch (UTMB) (N=5). The medical records of 13 of the 19 cases whose pathologic diagnosis was obtained only from the SCRP computer tape were reviewed, the remaining six records could not be found by hospital personnel. Medical records of the five cases whose pathologic diagnosis was obtained only from the UTMB computer tape were not checked because the recheck of all other abstracts had not revealed any serious discrepancies. All cases had a microscopically confirmed diagnosis of lung

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cancer and had been assigned an ICD code included in criteria for study eligibility. The histopathologic diagnosis of lung cancer for five cases of lung cancer was based on specimens obtained external to the respiratory system and adjacent lymph nodes (liver, small intestine, scalp, spinal cord, or brain tumor) and they were subsequently excluded from this study.

Interviews. The interview schedule was modified by the study staff from one previously used by the National Cancer Institute. Separate, but similar schedules were used to interview living study subjects and the next-of-kin of decedents (Appendix B, Schedule 1). Questions included in the interview schedule were intended to attain the objectives of the study and to reflect current knowledge concerning the design and structure of interview protocols. The focus and arrangement of each question was developed in consultation with all investigators concerned with the study as well as with consultants who had experience in other similar studies. Three pretests of the interview schedule were conducted with different groups at different times during the development phase.

Interviews were assigned to interviewers every two weeks by the field office which mailed preliminary, introductory letters to eligible respondents. Interviewers participated in tracing activities and used various sources to locate respondents, such as, city directories, telephone

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books, neighbors, newspaper obituaries, funeral homes, and nursing homes. Three hours or more were spent by some interviewers in tracing a respondent. A minimum of three attempts were made by interviewers on different days and at varying times of the day to arrange an appointment when respondents were not initially located. Interviews were usually reassigned to a second interviewer when respondents refused to be interviewed. The field office also forwarded additional encouraging, explanatory letters to respondents who initially expressed reluctance to participate in the study. Interviews lasting about 1 hour were conducted most frequently in the respondent's home by trained interviewers.

Quality control of Interviews. All completed interview schedules for the total six county project were reviewed by the Field Co-ordinator to identify any problems and were returned to the interviewer for correction when necessary. In the total six-county project, telephone validation of a sample of personal interviews (N = 221, 9.4%) was conducted. Questions selected from the interview schedule for validation pertained to the study subject's date of birth, usual occupation, consumption of milk, and whether the study subject ever smoked cigarettes. There were 25 (11.3%) discrepant responses pertaining to date of birth and the majority (16) differed by 1 year or less. Only one discrepancy occurred in regards to whether the study subject ever smoked cigarettes. Discrepancies pertaining to the usual occupation of the study subjects totalled 51 (25.1%).

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However, the question pertaining to usual occupation was phrased differently in the telephone interview than during the personal interview and some of the discrepancies reflect this difference. The same occupation described with either more or less detail occurred in 21 (10.3%) instances considered discrepant, a different occupation in the same industry was reported in 17 (8.4%), and a different occupation in a different industry occurred in 13 (6.4%) of the validations.

An additional 3% (N = 70) sample of personal interviews in the six-county project was selected for specific validation of information on smoking. Three questions from the smoking section in the interview schedule were repeated during the telephone interview. The percentage of similar responses to each question was: number of cigarettes smoked per day = 72.9%, age started to smoke = 41.4%, age stopped smoking = 72.9% (Appendix B, Table 2). Discrepant answers were almost equally divided for each question as to whether the telephone response was either a greater or smaller number than was obtained during the personal interview in the home. Discrepancies of 1 to 20 cigarettes occurred in 21 instances (more cigarettes were reported in the telephone interview than was reported in the personal interview in 12 instances and, in 9 instances, fewer cigarettes were reported by telephone respondents). The majority of discrepancies concerning the age at which persons started or stopped smoking cigarettes were differences of 5 years or less. Only responses obtained in a

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standardized manner by trained interviewers during personal interview in the home were used in the analysis.

Interview response rates. Of the 389 cases and 453 compeers eligible for interview, 69.7% of case and 62.3% of compeer interviews were completed (Table 7). A greater proportion of decedent case interviews (74.3%) was completed than was completed with living cases (52.9%). Among compeers, there was little difference in the proportion of interviews completed with next-of-kin (61.8%) and with living compeers (63.4%).

Reasons that interviews were not conducted included refusal by the person to be interviewed, study subject could not be located, lived outside the study area, or the interview was not accepted by the field office because field procedures had not been followed (Appendix B, Table 2). More than half (54.7%) of the overall nonresponse rate (34.3%)in the study was due to cases and compeers who were either not located or resided outside of the study area. Fewer cases (16.2%) than compeers (21.0%) were not located or resided outside the study area. Stratifying by vital status, more deceased (19.7%) than living (15.9%) cases and compeers were not located or lived outside the study area and deceased compeers contributed the highest proportion (24.0%) . More living cases (20.0%) than deceased cases (15.1%) could not be located or resided outside the study area. Refusal rates are slightly lower among case (13.6%) than among compeer

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interviews (15.9%), even including physicians' refusals for permission to interview 10 cases. The highest refusal rate occurred among living cases (27.1%) which included the 10 physician refusals and the lowest occurred among next-of-kin case interviews (9.9%). More living case interviews were not conducted than living compeer interviews due to physician and subjects refusals (27.1% versus 23.6%) but a higher proportion of the next-of-kin of compeers than cases refused interview (13.0% versus 9.9%). Similar proportions of case and compeer interviews were not conducted either because the individual could not be located (10.8% and 13.7%, respectively) or because they lived outside the study area (5.7% and 7.3%, respectively).

Data management

Coding

Data were coded by trained coders using a coding manual referent to the interview schedule. Lifetime occupational histories were coded using the Dictionary of Occupational Titles (DOT) (USDL, 1977) and industries were coded using the Standardized Industrial Classification Manual (SIC) (USOMB, 1972). Ten percent of all coding for the six-county area was recoded by a second coder. Discrepancies were resolved by supervisors who also recoded a sample of the work histories.

In addition to the review of coding by the six-county project, a 10% random sample (N=50) of personal interviews

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conducted with white female lung cancer cases (N = 26) and compeers (N = 24) in Harris County was recoded without prior knowledge of initial codes. There were no discrepancies in racial group, marital status, or ever/never smoked cigarettes. The county of last residence was incorrect in the initial code for two study subjects and two dates of birth had been coded incorrectly. A total of 141 occupations were recoded for 26 cases and 141 occupations for 24 compeers. A difference in the first 3 digits of the DOT code occurred in 57 (20.2%) of the occupations coded. However, the majority (N = 44, 77.2%) of these discrepancies in the first 3 digits either reflected differences between coding the wide variety of sales and clerical occupations, such as, "Bookkeeper, receptionist, secretary" = DOT codes 219 or 201, or else they reflected differences between the administrative aspect or technical aspect of the occupation, e.g., Merchandizer, buyer, supervised satellite stores" = DOT codes 185 or 219. A difference between the first three digits of the DOT code in which the occupation was notably changed occurred in only 13 (4.6%) codes. Overall, the proportions of 9 - digit occupational coding discrepancies were similar for cases (10.6%) and compeers (11.3%). The discrepancies were reviewed qualitatively and no serious discrepancies were noted in that the job title assigned by the first coder was similar, but not as specific as the code assigned by the second coder. No serious discrepancies were noted in the coding of industry.

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Data entry, editing and analysis. Interview data for the six-county study were entered directly into the computer. Entries were made twice during the initial entry and compared for agreement and accuracy. In addition to the initial entries, 10% of all data were re-entered and compared by a second person. Computer procedures for editing the data of the six-county project verified that numeric ranges were within reasonable limits, dates of residence and employment were in logical order, checked for consistency between record types, and determined if data had been omitted. Aspects of the data for cases and compeers in this study which had not been verified in the six-county project were also edited which resulted in the exclusion of seven cases (residence criteria not met = 6, poor quality of interview data = 1). Four compeers were also excluded (residence or ethnic criteria not met = 2, poor quality of interview data = 2). After data quality review, 259 cases and 278 compeers were retained in the analysis for this study. Data were stored in the Scientific Information Retrieval system (SIR, 1979). Data were analyzed with the Statistical Package for the Social Sciences (SPSS, 1975) and a microcomputer version of the Mantel-Haenszel odds ratio calculation (Grimson et al., 1980). In calculating odds ratios in which one or more cells included zero, an estimate of 0.5 was added to each of the four cells to permit the calculation (Hauck et al., 1982).

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Classification of occupations and industries as "high risk". Occupations and industries were identified as "high risk" exposures on the basis of results from previous studies of work areas suspected of being associated with the occurrence of lung cancer. Prior to analysis, occupations and industries were separately classified and listed as high risk (Appendix B, Tables 3 and 4).

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CHAPTER FOUR

Results

Demographic and Descriptive Variables

The majority of cases (78.0%) and compeers (75.5%) had lived in Harris County for more than 15 years and the average total duration of residence in the County since 1940 or later is similar for cases (26.3 years) and compeers (25.5 years) (Table 8). More than half of all cases (54.8%) and compeers (52.9%) were born in Texas and 90% of them were born outside of Harris County. Similar proportions of cases (46.9%) and compeers (48.9%) had lived on a farm or ranch prior to 16 years of age. Cases and compeers also had similar numbers of siblings (average of 3.6 and 3.8, respectively).

The usual occupation of the mothers of cases and compeers was in the Service category (82.5% and 86.5%, respectively) and these were chiefly housewife occupations (case mothers = 96.6% and compeer mothers = 94.5% in Service occupations) (Appendix C, Table 1). The numbers of mothers of cases and of compeers employed in any industry are small (50 and 49, respectively) which reflects the large

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proportions who were housewives and, consequently, not classified in the labor force. Service industries were the most frequent industry of mothers of cases (38.0%) and compeers (30.6%) (Appendix C, Table 2). The proportion of mothers employed in the Retail Trade industry was similar (20.0%) for both cases and compeers.

Similar proportions of the fathers of cases and of compeers had usually worked in agricultural, fishery, forestry, and related occupations (29.5% and 33.0%, respectively) as well as occupations classified as professional, technical, and managerial (18.7% and 16.0%, respectively). The Agricultural, Forestry, and Fishing industry comprised the largest single industry of fathers of both cases (29.5%) and compeers (32.6%). The Manufacturing industry occupied second position with 17.5% of cases' fathers and 15.9% of compeers' fathers thus employed.

The median year of birth for both cases and compeers was 1918 and the majority of cases (73.4%) and compeers (71.2%) were 50-69 years of age on January 1 1979 (Appendix C, Table 3). About 10% of cases and compeers were less than 50 years of age and 17% were 70 years of age or more. A greater proportion of cases (58.7%) than compeers (50.7%) were 50 to 64 years of age and a smaller proportion of cases (14.7%) than compeers (20.5%) were 65 to 69 years of age but differences between age groups are not statistically significant.

A greater proportion of cases (32.5%) than compeers

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(27.2%) had attained 13 or more years of schooling but the difference is not statistically significant (Table 8). A larger proportion of the husbands of cases (43.0%) than of compeers (34.5%) also had attained 13 or more years of education (Table 8).

Religious preferences prior to 16 years of age were primarily Protestant denominations with more cases than compeers professing that preference (86.1% versus 77.7%, respectively) (Table 8). More compeers (20.8%) than cases (11.4%) were Catholic and few cases (2.5%) and compeers (1.5%) were Jewish (Table 8).

A smaller proportion of cases (52.9%) than compeers (63%) were married (Table 8). Consequently, larger proportions of cases were widowed, divorced , or separated. The differences in marital status between cases and compeers are statistically significant. Cases, on average, had 1.7 children and compeers had 2.0. More compeers (17.3%) than cases (14.7%) had no children (Table 8).

Vital Status

The majority of cases (83.0%) and compeers (71.9%) were deceased and the difference in vital status between cases and compeers is statistically significant (Appendix C, Table 4). There is little difference by vital status of cases and compeers in the proportions who were born in Harris County but a significantly lower proportion of living cases (31.8%) than living compeers (50.0%) were born in

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TABLE 8

SUMMARY OF DESCRIPTIVE VARIABLES OF FEMALE LUNG CANCER CASES AND COMPEERS

Variables	Cases No.	Cases %	Mean, Median	Compeers No.	Compeers %	Mean Median
Born in:						
Texas	142	54.8		147	52.9	
Harris County	25	9.7		29	10.4	
Mean number years resided Harris County			26.3			25.5
Lived on a farm prior to 16 yr ago	119	46.9		132	48.9	
Median year of birth			1918			1918
Mean number siblings			3.6			3.8
Highest grade in school:						
0 - 12	170	67.5		195	72.8	
13 - 17	82	32.5		73	27.2	
Husband's schooling						
0 - 12	126	57.0		169	65.5	
13 - 17	95	43.0		89	34.5	
Religious preference:						
Protestant	211	86.1		206	77.7	
Catholic	28	11.4		55	20.8	
Jewish	6	2.4		4	1.5	
Marital status:						
Married	137	52.9		175	63.0	
Widowed	71	27.4		69	24.8	
Divorced	43	16.6		29	10.4	
Separated	4	1.5		1	.4	
Never married	4	1.5		4	1.4	
Mean number children			1.7			2.0

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Texas (Appendix C, Tables 5a, 5b). More similar proportions of deceased cases (59.5%) and compeers (54.0%) were born in Texas.

A significantly greater proportion of deceased cases (32.2%) than deceased compeers (23.6%) had attained 13 to 17 years of school (Appendix C, Table 6). However, among those living, a slightly smaller proportion of cases than compeers had attained 13 to 17 years of school (34.1% versus 36.4%).

Living cases and compeers differed significantly in marital status. Fewer living cases (52.3%) than compeers (71.8%) were married at time of interview and more living cases (25.0%) than compeers (5.1%) were divorced or separated (Appendix C, Table 7). Among deceased cases and compeers, differences in their marital status at time of interview are smaller and not statistically significant.

The age distributions among living cases and compeers differ from 2.6% to 8.6% within 10 year age groups but the overall difference is not statistically significant (Appendix C, Table 8). Similarly, among deceased cases and compeers, the age distributions differ by 2.6% to 6.7% within 10 year age groups and the difference is not statistically significant. The proportion of cases 65 or more years of age is lower among living (20.4%) than deceased (34.0%) and the difference is more marked between living compeers (20.5%) and deceased compeers (44.5%) 65 or more years of age.

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History of Smoking Cigarettes

The majority of cases (95.4%) and compeers (59.7%) had a history of smoking cigarettes and the majority of cases (71.4%) but less than half of the compeers (39.6%) were current smokers (Table 9). Compared with never-smokers, the odds ratios of developing lung cancer are: all smokers = 13.89, current smokers = 15.70, exsmokers = 10.33. Only two cases and two compeers had smoked cigars; no cases but two compeers had smoked a pipe. A summary of the cigarette smoking histories of the female lung cancer cases and their compeers is provided (Table 10).

Age started and stopped smoking cigarettes. The majority of cases (51.7%) but only 27.2% of compeers had started smoking cigarettes by 18 years of age (Appendix C, Table 9a,9b). The odds ratio for age at starting to smoke cigarettes compared with those who had never smoked increases from 9.33 for starting at 30 or more years of age to 17.76 for starting to smoke cigarettes between 6 and 16 years of age. Twice the proportion of cases (30.8%) than compeers (15.1%) had started smoking by 16 years of age. Among smokers, cases and compeers show similar patterns in the age at which they started to smoke except a higher proportion of cases (32.4%) than compeers (25.6%) started between 6 and 16 years of age (Figure 4) (Appendix C, Table 9b). Cases show a steep rise in the age at which they

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TABLE 9

SMOKING STATUS OF FEMALE LUNG CANCER CASES AND COMPEERS

Smoking status	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
All smokers	247	95.4	166	59.7	13.89	7.42	26.00	93.98	<.001
Current smoker	185	71.4	110	39.6	15.70	8.27	29.78	96.45	<.001
Exsmoker	62	23.9	56	20.1	10.33	5.15	20.73	50.33	<.001
Never smoked	12	4.6	112	40.3	1.00				
Total	259	100.0	278	100.0					

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TABLE 10

SUMMARY OF CIGARETTE SMOKING HISTORIES OF FEMALE LUNG CANCER CASES AND THEIR COMPEERS

Cigarette smoking history:	Cases	Compeers	Difference(1)	Odds Ratio(2)	
All smokers vs never smoked	95.4%	59.7%	35.7%	13.89	**
Current smokers vs never	71.4%	39.7%	31.7%	15.70	**
Exsmokers vs never	23.9%	20.1%	3.8%	10.33	**
Age started to smoke vs never smoked, all smokers					
30 + yr	9.1%	8.5%	0.6%	9.33	**
21 - 29 yr	18.6%	12.5%	6.1%	12.90	**
19 - 20 yr	15.8%	10.7%	5.1%	12.87	**
17 - 18 yr	20.9%	12.1%	8.8%	14.99	**
6 - 16 yr	30.8%	15.1%	15.7%	17.76	**
Age stopped smoking vs never smoked, all smokers					
19 - 37 yr	2.7%	7.7%	- 5.0%	1.44	n.s.
38 - 50 yr	11.0%	9.5%	1.5%	4.67	**
51 - 57 yr	28.8%	8.9%	19.9%	13.07	**
58 + yr	41.1%	7.1%	34.0%	23.33	**
Type of cigarette usually smoked vs never smoked, all smokers: Non-filter	18.7%	13.9%	4.8%	11.54	**
Filter	51.2%	28.6%	22.6%	15.44	**
Self-rolled	12.4%	3.3%	9.1%	33.19	**
Number of cigarettes per day vs never smoked, all smokers					
Less than 20	8.4%	15.2%	- 6.8%	4.67	**
20	30.4%	21.7%	8.7%	11.82	**
More than 20	56.4%	22.5%	33.9%	21.23	**
Number of years smoked vs never smoked, all smokers					
1 - 30 yr	20.7%	20.9%	- 0.2%	8.51	**
31 - 40 yr	38.6%	22.7%	15.9%	14.60	**
41 + yr	35.9%	15.4%	20.5%	20.00	**
Pack-years smoked vs never smoked, all smokers: 65.71 or more	37.1%	11.5%	25.6%	27.40	**

(1) Difference = Cases - Compeers.
** p = < 0.05
* n.s. = not significant at the 5% level.
NOTE: The percentage of cases and compeers in this table are percentages of all cases or all compeers.

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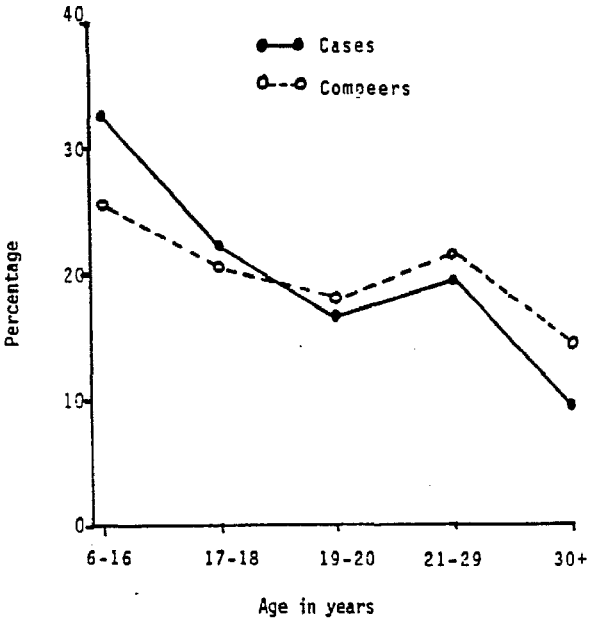

Figure 4. Age female lung cancer cases and compeers started to smoke cigarettes.

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stopped smoking cigarettes while compeers stopped smoking at much earlier ages (Figure 5) (Appendic C, Table 10a). Only 16.4% of cases but 51.8% of compeers had stopped smoking cigarettes by 50 years of age (Appendix C, Table 10b). Using cases and compeers who had never smoked cigarettes as a referent, the odds ratio of developing lung cancer increases from 1.44 to 23.33 as the age at which stopping cigarette smoking rises from 19 to 37 years of age to 58 or more years of age.

Type of cigarette smoked. Comparisons between smokers and never-smokers yield odds ratio estimates for the type of cigarette usually smoked which are markedly increased: non-filtertip = 11.54, filter-tip = 15.44, and self-rolled = 33.19 (Appendix C, Table 11). Among smokers, 53.8% of cases and 48.4% of compeers usually smoked filter-tip cigarettes while 27.6% of cases and 11.0% of compeers usually smoked self-rolled cigarettes.

Usual number of cigarettes smoked per day. The pattern of reporting the usual number of cigarettes smoked per day shows similar distributions among cases and compeers with 3 prominent peaks at 16 to 20, 26 to 30, and 36 to 40 number of cigarettes per day (Figure 6). These peaks probably reflect the tendency of respondents to report 1, 1.5, or 2 packs of cigarettes smoked per day. The majority of cases (91.2%) and compeers (74.4%) usually smoked 1 or more packs of cigarettes per day (average number of cigarettes: cases = 31.5, compeers = 24.6) (Appendix C,

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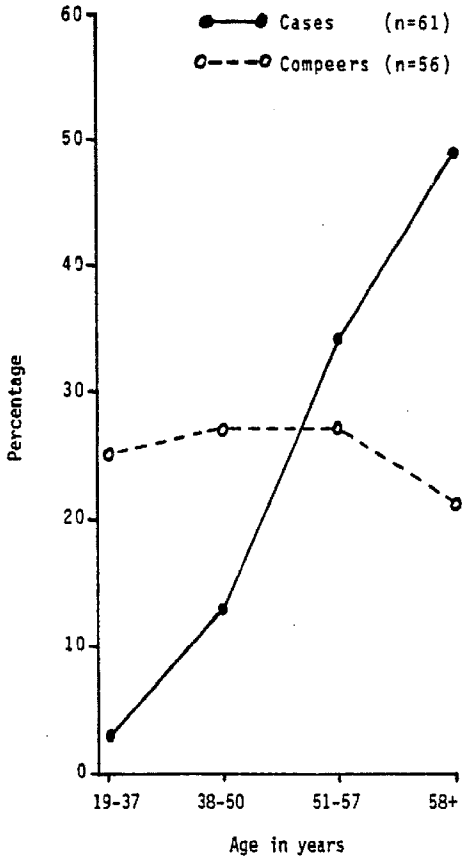

Figure 5. Age female lung cancer cases and compeers stopped smoking cigarettes.

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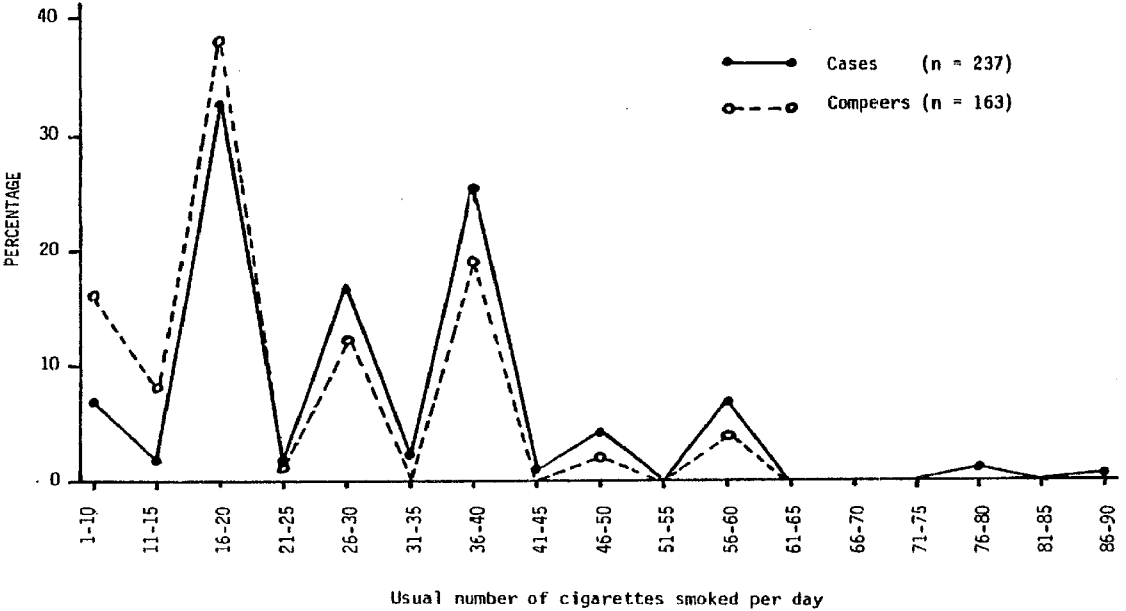

Figure 6. Usual number of cigarettes smoked per day by female lung cancer cases and compeers.

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Table 12). More than half of the cases (59.2%) but less than half of the compeers (37.8%) usually smoked more than 1 pack of cigarettes per day. Twenty cases (8.4%) and 6 compeers (3.7%) smoked more than 2.5 packs of cigarettes day. Among current smokers, 64.4% of cases and 44.6% of compeers smoked more than 1 pack of cigarettes per day. Current smokers among cases usually smoked an average of 5.6 more cigarettes per day than compeers while, among exsmokers, cases usually smoked an average of 8.9 cigarettes more per day than compeers. The odds ratio estimate among all smokers for the amount smoked, using never smokers as a referent, increases from 4.67 for smoking less than one pack per day to 21.23 for smoking more than one pack per day (Appendix C, Table 13).

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Duration smoked cigarettes. Among all smokers, the majority of cases (78.3%) and compeers (64.6%) smoked cigarettes for more than 30 years (average: cases = 37.3 years, compeers 32.2 years) (Figure 7) (Appendix C, Table 14). Current smokers among cases and compeers resemble each other in the length of time they smoked cigarettes (average number of years: cases = 37.9 years, compeers = 36.4 years) but, among exsmokers, the duration of smoking differs markedly between cases and compeers (Figure 8). Cases who were exsmokers smoked cigarettes an average of 12 years longer than compeers who were exsmokers (36.2 years and 24.0 years, respectively). Among exsmokers, the number of years cases smoked cigarettes shows a modest decline after 31 to

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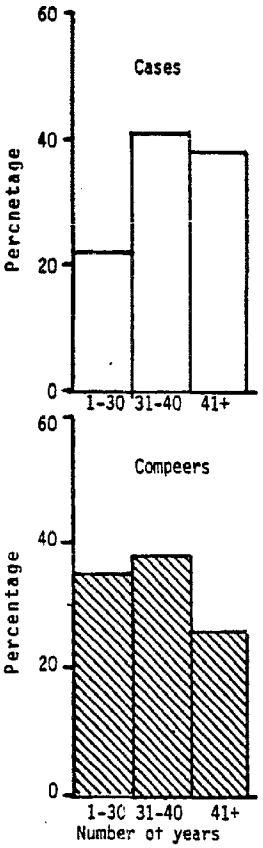

Figure 7. Duration female lung cancer cases and compeers smoked cigarettes.

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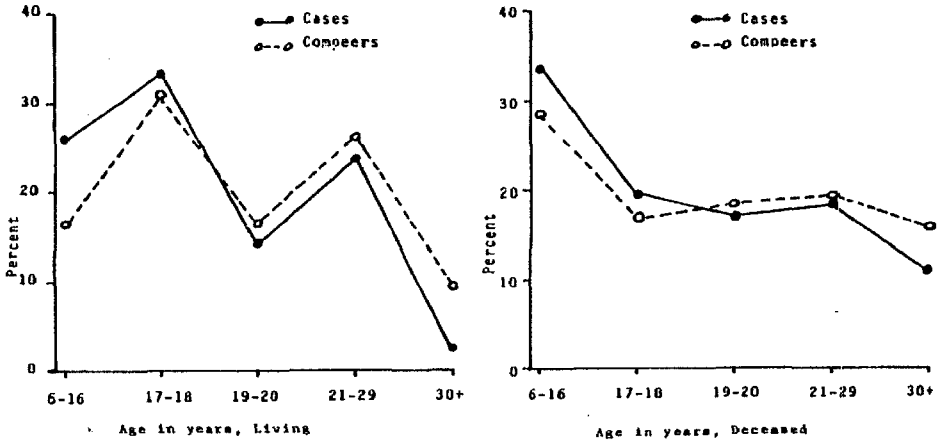

Figure 8. Age female lung cancer cases and compeers started to smoke cigarettes by vital status.

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40 years but compeers reflect a steep decline after 1 to 30 years. The odds ratio estimate among all smokers, using never smokers as a referent, for the number of years smoked increases from 8.51 for smoking 1 to 30 years to an odds ratio of 20.00 for smoking 41 or more years (Appendix C, Table 15).

Pack-years of cigarettes smoked. Pack-years of cigarettes smoked is estimated by multiplying the number of packs of cigarettes smoked per day by the number of years smoked. For example, smoking 0.82 packs per day for 20 years = 16.4 pack-years and smoking 2.2 packs per day for 20 years is equivalent to 44.0 pack-years. The majority of cases (65.7%) and less than half of the compeers (40.5%) had smoked 43.81 or more pack-years of cigarettes (Appendix C, Table 16). The proportion of cases (39.1%) who smoked 65.71 pack-years is twice the proportion of compeers (19.6%) who smoked this amount. The odds ratio among all smokers for pack-years smoked, using never smokers as a referent, shows an increase from 2.33 for smoking 1 to 16.42 pack-years to an odds ratio of 27.40 for smoking 65.71 or more pack-years. (Appendix C, Table 17).

Age of smokers. The majority of smokers were 50 to 64 years of age (cases = 59.9%, compeers = 55.4%). Among all smokers, fewer cases (9.7%) than compeers (12.7%) were 30 to 49 years of age and the difference is more pronounced among exsmokers: cases = 4.8%, compeers = 10.7% (Appendix C,

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Table 18).

Vital status and cigarette smoking. Among cases there is little difference in smoking status by vital status except among exsmokers: living = 43.2%, deceased = 20.0%. A larger proportion of living compeers (46.2%) than deceased compeers (38.0%) had never smoked cigarettes and a larger proportion of living (28.2%) than deceased (17.0%) compeers were exsmokers (Appendix C, Table 19).

More deceased than living cases started to smoke cigarettes at ages 6 to 16 years (33.7%, 26.2%, respectively), 19 or 20 years (17.1%, 14.3%, respectively), and at 30 or more years (11.1%, 2.4%, respectively) (Figure 8) (Appendix C, Table 20). Similarly, more deceased than living compeers started to smoke cigarettes at ages 6 to 16 years (28.8%, 16.7%, respectively), 19 or 20 years (18.6%, 16.7%, respectively), and at 30 or more years (16.1%, 9.5%, respectively).

The majority of living cases who stopped smoking cigarettes, did so between 51 and 57 years of age while the majority of deceased cases stopped smoking after 58 years of age (Figure 9) (Appendix C, Table 21). The majority of living compeers who stopped smoking (63.6%) had stopped by 50 years of age while the majority of deceased compeers (55.9%) stopped smoking cigarettes after 50 years of age.

Proportional distributions of the usual number of cigarettes smoked per day show peaks among both living and deceased cases and compeers noted earlier at 16 to 20, 21 to

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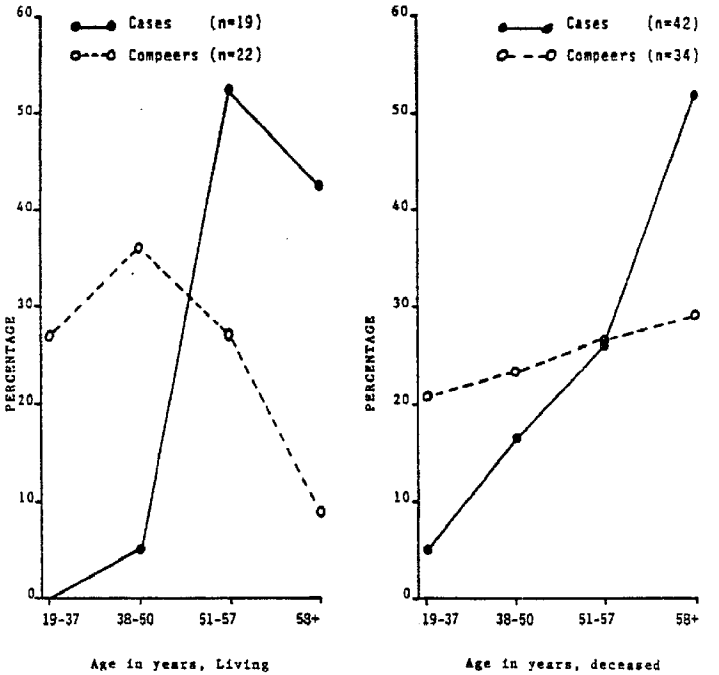

Figure 9. Age female lung cancer cases and compeers stopped smoking cigarettes by vital status.

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30, and 36 to 40 cigarettes per day. Both living and deceased cases smoked an average of 2.5 packs of cigarettes per day (31.7 cigarettes and 31.5 cigarettes, respectively) (Appendix C, Table 22). Living compeers smoked an average of 1 pack per day while deceased compeers smoked an average of 1.3 packs of cigarettes per day. The difference in the number of cigarettes usually smoked per day is less for living than for decedent study subjects in all three categories. Living and decedent cases had similar patterns for duration of smoking but deceased compeers tended to smoke for longer periods of time than living compeers (Appendix C, Table 23).

Age distributions for case and compeer smokers classified by smoking status and vital status reflect no statistical differences in age for cases versus compeers or for living versus deceased subjects (Appendix C, Table 24).

Proportional distributions of pack-years of cigarettes smoked are similar between living and deceased cases with 24.4% of living cases and 21.9% of deceased cases having smoked less than 34.22 pack-years of cigarettes and both showing a constant, steep increase in amount of pack-years smoked beginning with 34.22 pack-years (Figure 10) (Appendix C, Table 25). Between living and deceased compeers, however, there are marked differences in proportional distributions of pack-years of cigarettes smoked. Living compeers show a constant decline in pack-years of cigarettes smoked beginning with 35.7% of them having smoked less than 16.43 pack-years. Deceased compeers,

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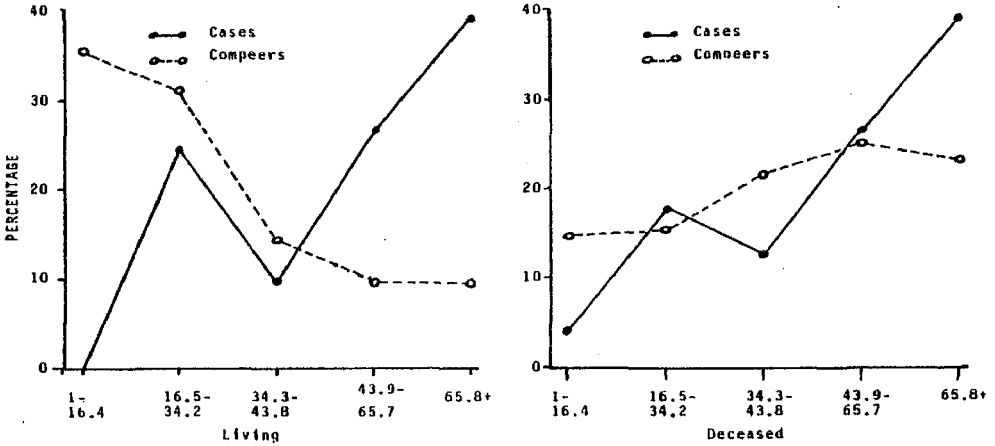

Figure 10. Pack-years of cigarettes smoked by female lung cancer cases and compeers by vital status.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

on the other hand, show an almost constant increase in pack-years of cigarettes smoked beginning with about 15% of them having smoked less than 16.43 pack-years to 23.3% with a history of smoking 65.71 or more pack-years of cigarettes.

Odds ratio estimates for most smoking variables are higher among living cases and compeers than among deceased, except for nonfilter-tip use (9.00 and 11.99, respectively), and smoking for 1 to 30 years (5.14, 9.71, respectively) (Table 11) (Appendix C, Tables 26 to 33). The lower odds ratio estimates among decedent cases and compeers are due to the greater amount of smoking among deceased than living compeers.

Demographic variables by smoking status. Proportional differences in smoking status among cases by place of birth, religious preference, or marital status are negligible because almost all of them had a history of smoking cigarettes. The proportion of compeers who had never smoked cigarettes is higher in Texas (47.6%) but lower in Harris County (41.4%) than among compeers born elsewhere (Appendix C, Table 34). The proportion of cases whose religious preference prior to 16 years of age was Protestant is about 10% higher than among compeers and, when adjusted for smoking status, yields a significant odds ratio of 2.13 (Appendix C, Table 35). Among smokers, religious preference is associated with risk of lung cancer whereas religious preference is not associated with risk of lung cancer among never-smokers. Among cases, smoking is associated with

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TABLE 11

SUMMARY OF CIGARETTE SMOKING HISTORY BY VITAL STATUS OF FEMALE LUNG CANCER CASES AND COMPEERS: ODDS RATIOS, 95% CONFIDENCE INTERVALS, AND CHI-SQUARE ESTIMATES.

Cigarette smoking history	*Living Cases and Compeers* Odds Ratio	Confidence Intervals	Chi-Square	*Deceased Cases and Compeers* Odds Ratio	Confidence Intervals	Chi-Square
Smoking status:						
All smokers vs. never	18.00	(4.07, 79.61)	20.81*	12.56	(6.26, 25.20)	68.13*
Current vs. never	20.70	(4.42, 97.03)	19.79*	13.68	(6.74, 27.77)	69.05*
Exsmoker vs. never	15.55	(3.30, 73.28)	15.01*	9.61	(4.33, 21.35)	34.21*
Age started to smoke, all smokers vs never smokers:						
6 to 16 yr age	28.29	(5.11,156.46)	21.37*	14.98	(6.88, 32.60)	57.40*
Age standardized	17.53#	(8.81, 34.86)	66.63*	12.57#	(8.91, 17.75)	207.02*
Age stopped smoking, all smokers vs never smokers:						
58 or more yr age	72.00	(8.78,590.56)	26.81*	16.72	(6.17, 45.30)	38.50*
Age standardized	13.84#	(6.12, 31.29)	39.85*	8.97#	(5.29, 15.21)	66.27*
Type of cigarette usually smoked vs never smoked						
Non-filter	9.00	(1.60, 50.69)	7.86*	11.99	(5.27, 27.27)	41.64*
Filter	20.45	(4.41, 94.92)	22.27*	14.11	(6.77, 29.44)	64.08*
Self-rolled	102.20	(4.05,2579.50)	19.87*	24.49	(9.04, 66.37)	51.15*
Number of cigarettes per day vs never smoked, all smokers						
Less than 20	4.80	(0.80, 29.07)	3.35	4.79	(1.95, 11.72)	12.90*
20	15.88	(3.26, 77.43)	16.36*	10.78	(5.01, 23.20)	44.48*
More than 20	39.60	(7.93,197.75)	31.08*	17.39	(8.34, 36.29)	76.90*
Number of years smoked vs never smoked, all smokers						
1 - 30 yr	5.14	(0.95, 27.83)	4.21*	9.71	(4.41, 21.41)	37.35*
31 - 40 yr	29.57	(6.14,142.32)	27.31*	11.72	(5.52, 24.87)	50.36*
41 or more yr	33.43	(6.14,182.01)	24.39*	16.72	(7.73, 36.15)	64.44*
Pack-years vs never smoked Standardized	15.95#	(8.41, 30.26)	71.94*	11.61#	(8.18, 16.47)	188.58*

= Mantel-Haenszel estimate.
* = Significant at the 5% level or less.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

religious preference which may explain this association. Cases and compeers who had attained 0 to 12 years of school had a higher proportion of smokers (68.0%, 71.9%, respectively) than those who had attained higher grades (Appendix C, Table 36). The highest proportions of smokers by marital status of compeers are among those who were divorced (72.4%) or married (62.9%). The odds ratio is elevated for cases who were not married at time of interview and remains significant when standardized for smoking (1.63) (Appendix C, Table 37). Among smokers, marital status is associated with risk of lung cancer whereas marital status is not associated with risk of lung cancer among never-smokers. Among cases, marital status is associated with risk of lung cancer which may explain the association.

Usual Occupation

The usual occupation of cases and compeers is described in two ways: (1) the longest duration employed in a single occupation determined by a review of work histories and, (2) the occupation reported by respondents as having been the usual lifetime occupation of cases and of compeers. The most frequent usual occupation, determined either by longest duration employed or as reported by respondents, of both cases and compeers in all age groups was a Service occupation (Figure 11) (Appendix C, Table 38).

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Longest duration employed in an occupation.

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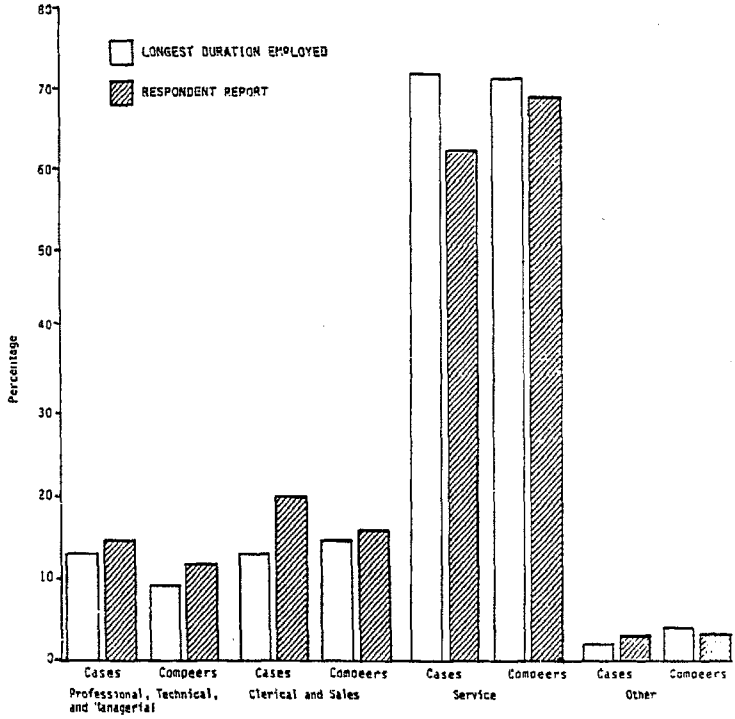

Figure 11. Usual occupation of female lung cancer cases and compeers as determined by longest duration employed and as reported by respondents.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Occupations in which the majority of cases (72.3%) and compeers (71.4%) were employed for the longest period of time, as determined by a review of work histories, were in the Service category (Appendix C, Table 38). The Service category was comprised mostly of the occupation of housewife and a smaller proportion of cases (85.1%) than compeers (92.2%) was employed for the longest duration in this capacity. Housewife as a usual occupation determined by longest duration employed comprised about two-thirds of all usual occupations of cases (61.6%) and of compeers (65.8%). Two additional categories comprised most of the remaining usual occupations determined by the longest duration employed: Clerical and Sales (cases = 13.2%, compeers = 15.6%) and Professional, Technical, and Managerial occupations (cases = 12.8%, compeers = 9.3%).

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Usual occupation reported by respondents. The usual occupation reported by respondents tended to be under-reported in Service occupations and over-reported in other occupations for both cases and compeers. Over-reporting, which was generally greater among cases than compeers, occurred primarily in the Clerical and Sales and the Professional, Technical, and Managerial categories. A lower proportion of cases than compeers reported usual occupation in the Service category than was identified as the longest duration employed from the work histories (cases = 62.6%, compeers = 69.1%) and the difference was greater among cases (9.8%) than among compeers (2.3%). However, the proportion

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

of housewife occupations within the Service category among cases (84.4%) and compeers (91.6%) as reported by respondents were similar to those determined in the Service category by the longest duration employed. Among all usual occupations, "housewife" was reported by respondents as a usual occupation less frequently than was determined by longest duration employed and the difference was greater among cases (8.9%) than among compeers (2.5%). Larger proportions of cases and compeers reported usual occupation in the Clerical and Sales category than were determined by the longest duration employed and this was more noticeable for cases (6.7%) than for compeers (1.1%).

Usual occupation by age. Across all age groups of both cases and compeers, determined either by the longest duration employed or as reported by respondents, the most frequent category of usual occupation was the Service category (Appendix C, Table 39). Excluding the 30 to 39 year age group in which the numbers are too small for comparison, the Service category comprised from 55.0% to 80.5% of all usual occupations within the different age groups. The highest proportions of usual occupations in the Service category, determined both by the longest duration employed and as reported by respondents, was primarily among cases and compeers 70 years of age or more. The lowest proportion of usual occupations in the Service category (55.0%) occurred among those reported by respondents for cases 50 to

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

59 years of age. This proportion (55.0%) was 21.9% lower than the proportion in the Service category determined by the longest duration employed (76.8%) for this same age group of cases and was the largest proportional difference between the two methods of identifying usual occupations for any age group among both cases and compeers. In the 50 to 59 year age group, there were proportionally more usual occupations in the Clerical and Sales category among cases than compeers determined both by longest duration employed (4.3%) and as reported by respondents (9.6%). In contrast, there were proportionally fewer usual occupations in the Professional, Technical, and Mangerial category among cases than compeers determined by longest duration employed (6.7%) in the 50 to 59 year age group.

Usual occupation by vital status. Usual occupations according to the vital status of cases and compeers, determined by longest duration employed and as reported by respondents, show different patterns between cases and compeers (Appendix C, Table 40). In Service occupations, for example, respondents reported similar proportions of cases employed (living cases = 59.1%, deceased cases = 63.2%) and similar proportions of cases were determined by the longest duration employed to be in Service occupations (living cases = 75.0%, deceased cases = 71.8%). For cases, the proportional differences are greater between reported occupations in the Service category and those determined by longest duration (living = 15.9%, deceased = 8.6%).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Compeers, however, show similar proportions of cases employed in the Service category among living (longest duration = 64.9%,) and deceased (longest duration = 75.0%) subjects. Compeers show greater proportional differences by vital status (longest duration employed = 9.1%). The differences suggest that, among cases, respondents' reports of occupations differ from those determined by longest duration employed while, among compeers, the greatest difference is between the occupations of those living or deceased. The difference in occupations by the vital status of compeers seems reasonable due to the older age of decedent study subjects and age patterns of employment. The difference between respondents reports of usual occupations and those determined by the longest duration employed for cases, however, suggests a reporting bias. In this example, there seems to have been a tendency for Service occupations to be underreported among cases, particularly among living cases. Thus, only the more objective method of assessing duration will be used in the analysis.

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Usual occupation by smoking status. Throughout all categories of usual occupations reported, 90.3% to 100.0% of cases had a history of smoking cigarettes (Appendix C, Table 41). Among compeers in the various occupational categories those with a usual occupation in Professional, Technical, and Managerial occupations have the highest proportion of cigarette smokers (68.0%, 65.56%,

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

respectively), followed by Service occupations (59.4%, 59.5%, respectively), and Clerical and Sales (54.8%, 56.5%, respectively). The number of compeers with a usual occupation in other categories is too small to be reflective of patterns of cigarette smoking.

Usual Industry

Usual industry of employment was determined by a review of work histories, for the longest duration employed in a specific industry. The usual industries of cases and compeers were similarly distributed (Figure 12) (Appendix C, Table 42). A large proportion of the usual industry of employment for both cases (40.2%) and compeers (50.2%) were classified as "unemployed, retired, disabled, or on welfare" which is chiefly a reflection of the large number of housewives who are not classified in the labor market. Service industries comprised the largest single industry in which study subjects were employed for the longest period of time (cases = 39.2%, compeers = 39.9%). A large proportion of cases (26.1%) and compeers (24.6%) were employed in Retail Trade industries. The usual industry for 4 percent of cases was either the Mining or Construction industry. Neither of these industries was identified as a usual industry for any compeer.

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Usual industry by age. Across age groups, the Services industry comprised the largest single proportion

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

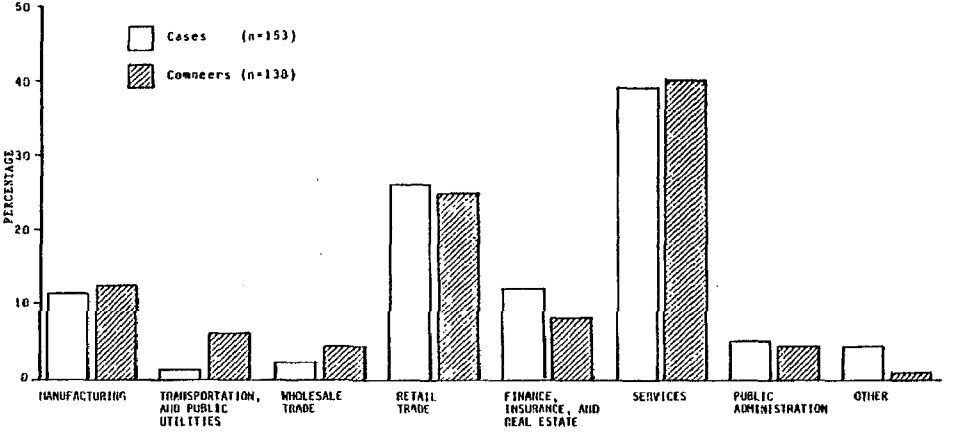

Figure 12. USUAL INDUSTRY OF FEMALE LUNG CANCER CASES AND COMPEERS AS DETERMINED BY LONGEST DURATION EMPLOYED.*

* Unemployed, disabled, retired, or on welfare: Cases = 40.2%, Compeers = 50.2%.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

of usual industries of both cases and compeers, except for five cases in the age group 40 - 49 years in which Retail Trade comprised more than 30% of the usual industries (Appendix C, Table 43). Retail Trade was the second most common industry in all age groups of cases and compeers. There were four cases and no compeers 40-49 years years of age who had a usual industry in Manufacturing, three cases and no compeers 50 - 59 years of age in Construction, and three cases and no compeers 60 - 69 years of age with a usual industry in the Mining industry.

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Usual industry by vital status. The industries in which cases and compeers were usually employed are similar according to their vital status and do not differ significantly (Appendix C, Table 44). A greater proportion of living cases than deceased cases had been employed in Manufacturing (12.0% and 10.9%, respectively), Retail Trade (32.0% and 25.0%, respectively), and Public Administration (8.0% and 3.9%, respectively). A greater proportion of living compeers than deceased compeers had been employed in the Manufacturing (17.6% and 9.2%, respectively), Services (41.2% and 39.1%, respectively), and in Public Administration industries (5.9% and 3.4%, respectively).

Usual industry by smoking status. From 95.0% to 100.0% of cases employed in industry had a history of smoking cigarettes (Appendix C, Table 45). The proportions of cigarette smokers in industries employing 10 or more

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

compeers were: Finance, Insurance, and Real Estate = 90.9%, Retail Trade = 70.6%, Services = 63.6%, and Manufacturing = 58.8%.

Employment in a High Risk Industry and/or a High Risk Occupation

The selection of occupations and industries as "high risk" is based primarily on occupations and industries determined by previous studies to be potentially associated with the occurrence of lung cancer, particularly in men (Appendix B, Tables 1 and 2). A summary of odds ratio estimates for employment in high risk industries and/or high risk occupations is provided (Table 12).

Employment in either a high risk industry or a high risk occupation

The majority of cases (63.3%) and compeers (57.9%) had been employed in either a high risk industry or high risk occupation (Figure 13). The odds ratio for employment in either a high risk industry or occupation compared with cases and compeers never employed in a high risk industry or occupation is 1.25 which is elevated but not statistically significant (Appendix C, Table 46). Almost all cases (98.2%) and the majority of compeers (63.4%) who had been employed in either a high risk industry or occupation had a history of smoking cigarettes. The age-stratified odds ratios for

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

TABLE 12

SUMMARY OF HISTORY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY AND/OR A HIGH RISK OCCUPATION: ODDS RATIOS, 95% CONFIDENCE INTERVALS, AND STATISTICAL SIGNIFICANCE.

Employment in a high risk	Odds ratio	95% Confidence Interval Low	High	Chi-Square p value
Occupation or a high risk industry				
Ever vs never	1.25	0.89	1.78	n.s.**
Age standardized	1.22*	0.85	1.74	n.s.
Smoking standardized	1.05*	0.70	1.51	n.s.
Age and smoking standardized	1.08*	0.74	1.59	n.s.
Age and pack-years standardized	1.04*	0.67	1.61	n.s.
Industry				
Ever vs never	1.32	0.94	1.85	n.s.
Age standardized	1.28*	0.90	1.81	n.s.
Smoking standardized	1.07*	0.74	1.57	n.s.
Age and smoking standardized	1.12*	0.77	1.64	n.s.
Employed once or more vs never employed	1.54*	1.03	1.74	< 0.05
Age standardized	1.29*	0.96	1.73	n.s.
Smoking standardized	1.13*	0.84	1.52	n.s.
Employed one year or more vs never employed	1.54*	1.02	1.77	< 0.05
Age standardized	1.35*	.99	1.83	n.s.
Smoking standardized	1.14*	0.84	1.55	n.s.
Time period employed				
Prior to 1969	1.27	0.90	1.78	n.s.
Smoking standardized	1.04*	0.72	1.52	n.s.
Prior to 1959	1.36	0.97	1.92	n.s.
Smoking standardized	1.24*	0.85	1.81	n.s.
Prior to 1949	1.27	0.89	1.54	n.s.
Smoking standardized	1.16*	0.78	1.72	n.s.

Employment in a high risk	Odds ratio	95% Confidence Interval Low	High	Chi-Square p Value
Occupation#				
Ever vs never	1.30	0.89	1.90	n.s.
Age standardized	1.25*	0.85	1.83	n.s.
Smoking standardized	1.21*	0.79	1.85	n.s.
Age and smoking standardized	1.24*	0.82	1.90	n.s.
Employed once or more vs never employed	1.29*	0.92	1.82	n.s.
Age standardized	1.30*	0.91	1.85	n.s.
Smoking standardized	1.24*	0.85	1.83	n.s.
Employed one year or more vs never employed	1.33*	0.93	1.89	n.s.
Age standardized	1.34*	0.92	1.93	n.s.
Smoking standardized	1.31*	0.87	1.96	n.s.
Time period employed				
Prior to 1969	1.26	0.86	1.86	n.s.
Smoking standardized	1.14*	0.73	1.76	n.s.
Prior to 1959	1.22	0.81	1.85	n.s.
Smoking standardized	1.12*	0.70	1.79	n.s.
Prior to 1949	1.61	1.01	2.56	n.s.
Smoking standardized	1.24*	0.75	2.06	n.s.
Occupation and a high risk industry#				
Ever vs never	1.49	0.99	2.26	n.s.
Age standardized	1.43*	0.95	2.16	n.s.
Smoking standardized	1.34*	0.84	2.13	n.s.
Age and smoking standardized	1.36*	0.86	2.15	n.s.
Age and pack-years standardized	1.42*	0.85	2.37	n.s.

* Mantel-Haenszel odds ratio estimate.
** n.s. = Chi-square not significant at the 5% level.
\# All cases ever employed in a high risk occupation and both a high risk occupation and a high risk industry had a history of cigarette smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

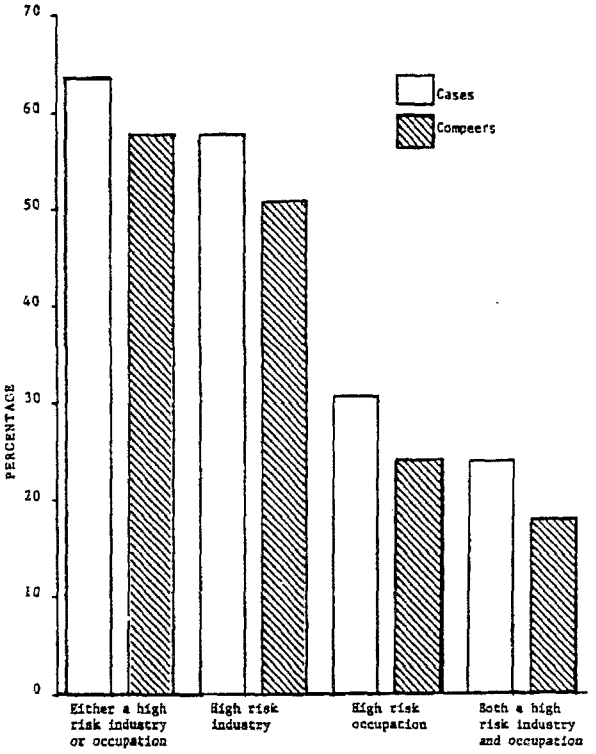

Figure 13. Female lung cancer cases and compeers ever employed in either a high risk industry or a high risk occupation, a high risk industry, a high risk occupation, or both a high risk industry and a high risk occupation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

employment in either a high risk industry or occupation (1.22) as well as the smoking-adjusted odds ratio (1.08) are slightly elevated but not statistically significant (Appendix C, Tables 47 and 48). Stratifying by age and pack-years smoked for cases and compeers ever employed in either a high risk industry or occupation, using those never employed in a high risk occupation or industry as a referent, yields an odds ratio of 1.04 which is not statistically significant (Appendix C, Table 49).

Employment in a high risk industry

A larger proportion of cases (57.9%) than compeers (51.1%) had worked in a high risk industry (Figure 13). The odds ratio for ever versus never employed in a high risk industry is 1.32 which is not statistically significant (Appendix C, Table 50). Almost all cases (98.0%) and the majority of compeers (64.8%) employed in a high risk industry had a history of smoking cigarettes and adjusting for smoking yields an odds ratio of 1.07. Stratifying cases and compeers ever employed in a high risk industry by age, and using those never employed in a high risk industry as a referent, yields an odds ratio of 1.28 which is not statistically significant (Appendix C, Table 51). However, in persons 55-59 years of age a significantly greater proportion of cases (26.0%) than compeers (18.3%) had been employed in a high risk industry (odds ratio = 2.57, statistically significant). Stratifying by age and smoking

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

status yields a slightly elevated odds ratio (1.12) which is not statistically significant (Appendix C, Table 52).

The average frequency of employment in a high risk industry is similar among cases (2.3) and compeers (2.1) but more cases (61.3%) than compeers (52.8%) had been employed more than once in a high risk industry (Figure 14) (Appendix C, Table 53). The odds ratios for frequency of employment in a high risk industry, compared with those never employed in a high risk industry, stratified by age (1.29) and by smoking (1.13), although elevated, are not statistically significant (Appendix C, Tables 54 to 56). The average number of years cases were employed in a high risk industry is longer than that of compeers (10.3 and 8.7, respectively) and more cases (52.5%) than compeers (44.4%) had worked longer than 5 years in a high risk industry (Figure 15) (Appendix C, Table 57). Cases and compeers employed for one year or more in a high risk industry compared with those never employed in a high risk industry is 1.34 which is statistically significant (Appendix C, Table 58). However, the odds ratio estimates for duration of employment in a high risk industry, compared with those never employed in a high risk industry, stratified by age (1.29) and by smoking (1.13), although elevated, are not statistically significant (Appendix C, Tables 59 and 60).

The majority of cases (70.2%) and compeers (67.4%) ever employed in a high risk industry had been employed in one prior to or during 1949 (Appendix C, Table 61).

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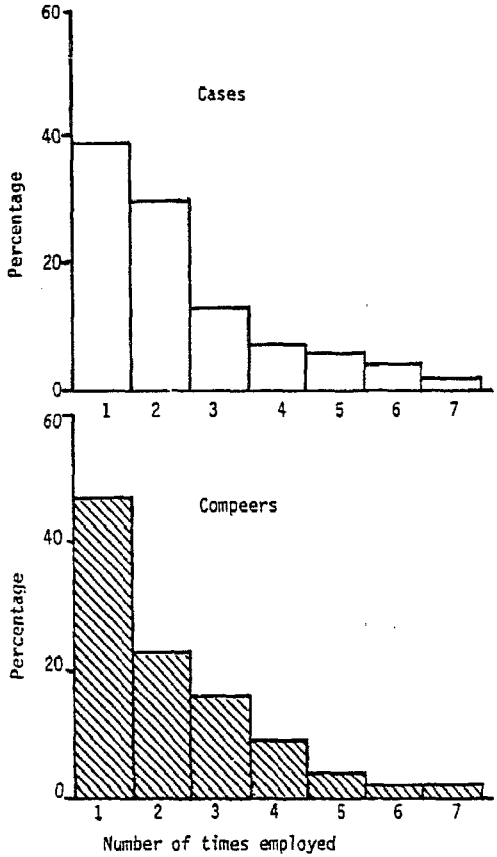

Figure 14. Frequency female lung cancer cases and compeers were employed in a high risk industry.

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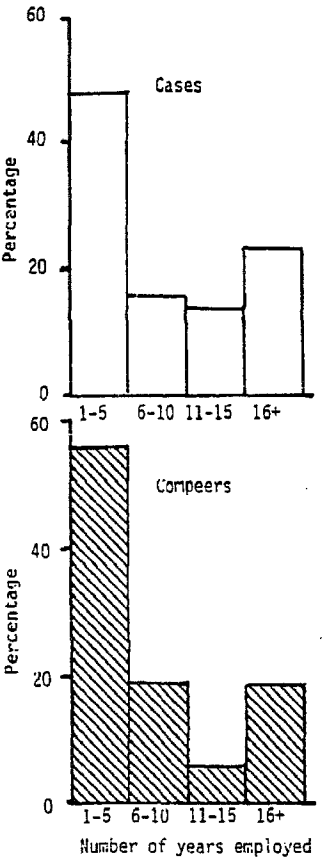

Figure 15. Duration female lung cancer cases and compeers were employed in a high risk industry.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

However, the odds ratio estimate, adjusted for smoking and using those never employed in a high risk industry as a referent group, is only slightly elevated (1.16) and is not statistically significant. The odds ratios for employment in a high risk industry prior to or during 1959 (1.24) or 1969 (1.04) are also elevated but not statistically significant when adjusted for smoking status.

Employment in a high risk occupation

A slightly greater proportion of cases (30.5%) than compeers (25.2%) had been employed in a high risk occupation (Figure 13) yielding an odds ratio of 1.30 which is not statistically significant when compared with those never employed in a high risk occupation (Appendix C, Table 62). The age-stratified odds ratio is slightly lower (1.25) (Appendix C, Table 63). All cases and 60.0% of compeers who had worked in a high risk occupation had a history of smoking cigarettes and adjusting for smoking status for employment in a high risk occupation yields an odds ratio of 1.21. Stratifying by age and smoking among cases and compeers ever employed in a high risk occupation yields an odds ratio (1.24) similar to the previous estimates for employment in a high risk occupation (Appendix C, Table 64). Smoking- adjusted odds ratios for employment in a high risk occupation are unstable because of no cases employed who never smoked.

The majority of cases (53.2%) and a large proportion

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of compeers (42.9%) had worked only once in a high risk occupation and a slightly higher proportion of cases (10.1%) than compeers (7.1%) had been employed 5 or more times in a high risk occupation (Figure 16) (Appendix C, Table 65). The average number employments in a high risk occupation is similar between cases (2.1) and compeers (2.2). The odds ratios for frequency of employment in a high risk occupation, compared with those never employed in a high risk occupation, stratified by age (1.30) and by smoking (1.24), although elevated, are not statistically significant (Appendix C, Tables 66 to 68). More cases (39.7%) than compeers (28.6%) had worked for 1 to 3 years and more cases (37.0%) than compeers (30.2%) had been employed for 10 or more years in a high risk occupation (Figure 17) (Appendix C, Table 69). The average number of years cases and compeers were employed in a high risk occupation is longer among cases (9.9 and 8.7 years, respectively). The odds ratio estimates for duration of employment in a high risk occupation, compared with those never employed in a high risk occupation, stratified by age (1.34) and by smoking (1.31), although elevated, are not statistically significant (Appendix C, Tables 70 to 72).

The majority of cases (63.3%) and compeers (51.4%) ever employed in a high risk occupation had been employed in one prior to or during 1949 (Appendix C, Table 73). However, the smoking-adjusted odds ratio, using cases and compeers never employed in a high risk occupation as a referent group, is only slightly elevated (1.24) and is not

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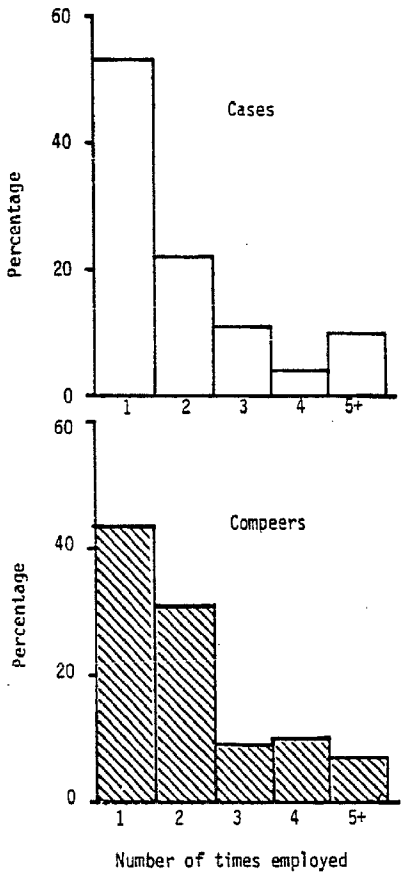

Figure 16. Frequency lung cancer cases and compeers were ever employed in a high risk occupation

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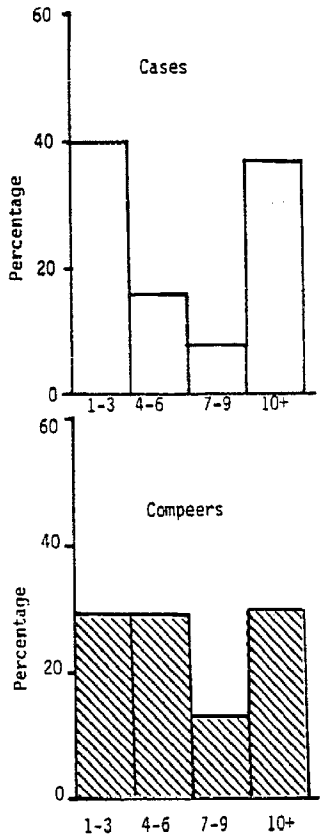

Figure 17. Duration female lung cancer cases and compeers were employed in a high risk occupation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

statistically significant. The odds ratios for employment in a high risk occupation prior to or during 1959 (1.12) or 1969 (1.14) are also low and not statistically significant when adjusted for smoking status.

Employment in both a high risk industry and a high risk occupation

A greater proportion of cases (25.1%) than compeers (18.3%) had been employed in both a high risk industry and a high risk occupation (Figure 13). Only seven cases and three compeers had ever been employed simultaneously in both a high risk industry and a high risk occupation. The odds ratio estimates for employment in both a high risk industry and a high risk occupation, although not significant at the 5% level, are the highest ratios for employment in high risk industries or occupations. All cases ever employed in both a high risk industry and a high risk occupation had smoked cigarettes. Ever employed in both a high risk occupation and industry, compared with never employed in a high risk occupation or industry, yields an odds ratio of 1.49 (Appendix C, Table 74). Stratifying by age and by smoking yields elevated but not statistically significant odds ratios (1.43 and 1.34, respectively) (Appendix C, Table 75). Stratifying by both age and smoking for employment in both a high risk industry and occupation yields an odds ratio of 1.36 and, when stratified by age and pack-years the odds ratio is 1.42 which is not statistically significant

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(Appendix C, Tables 76 and 77).

No study subject under 40 years of age had been employed in both areas. Over all age groups, differences between cases and compeers employed in both high risk industries and high risk occupations are significant at the 10% level (Mantel-Haenszel odds ratio: 1.43). Odds ratios are elevated in the age groups 45 to 49 years (1.62), 50 to 54 years (2.65), 55 to 59 years (2.12) years, and in those 70 years of age or more (3.17) but none are significant at the 5% level.

Employment in a high risk industry and/or a high risk occupation by vital status

Odds ratio estimates for employment in a high risk occupation are generally lower among living than deceased cases and compeers (Table 13) (Appendix C, Tables 78 to 91). Among decedents, the frequency and duration of employment in a high risk industry yield elevated and statistically significant odds ratios (1.48 and 1.47, respectively) but, when adjusted for smoking status they are decreased (1.25 and 1.27, respectively) and lose significance.

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Additional Variables

Several additional variables, such as family history of lung cancer, alcohol consumption, use of hair spray, use of a hand-held hair dryer, residing with a household member

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

TABLE 13

SUMMARY OF HISTORY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY AND/OR A HIGH RISK OCCUPATION BY VITAL STATUS: ODDS RATIOS, 95% CONFIDENCE INTERVALS, AND STATISTICAL SIGNIFICANCE

Variables	Living Cases and Compeers				Deceased Cases and Compeers			
	Odds Ratio	Confidence Intervals	Chi-Square	p Value	Odds Ratio	Confidence Intervals	Chi-Square	p Value
Employment in high risk occupation or high risk industry:								
Ever/never	1.07	(0.49, 2.36)	.03	n.s.	1.41	(0.95, 2.09)	2.94	n.s.
Smoking standardized	0.86#	(0.37, 2.01)	.12	n.s.	1.12#	(0.73, 1.73)	0.27	n.s.
Employment in a high risk industry:								
Ever/never	1.16	(0.55, 2.48)	.16	n.s.	1.42	(0.96, 2.09)	3.16	n.s.
Once or more vs never	1.15#	(0.66, 1.99)	.24	n.s.	1.48#	(1.09, 2.01)	6.40	< 0.05
Smoking standardized	0.98#	(0.52, 1.84)	.01	n.s.	1.25#	(0.88, 1.76)	1.60	n.s.
One year or more vs never	1.19#	(0.66, 2.15)	.35	n.s.	1.47#	(1.07, 2.02)	5.52	< 0.05
Smoking standardized	1.03#	(0.53, 1.98)	.01	n.s.	1.27#	(0.89, 1.81)	1.74	n.s.
Employment in a high risk occupation:								
Ever/never	1.24	(0.56, 2.73)	.28	n.s.*	1.38	(0.89, 2.14)	2.08	n.s.
Once or more vs never	1.24#	(0.60, 2.56)	.33	n.s.	1.38#	(0.92, 2.08)	2.40	n.s.
Smoking standardized	1.42#	(0.62, 3.22)	.69	n.s.	1.23#	(0.78, 1.94)	0.81	n.s.
One year or more vs never	1.24#	(0.62, 2.48)	.36	n.s.	1.45#	(0.95, 2.21)	3.03	n.s.
Smoking standardized	1.40#	(0.63, 3.08)	.69	n.s.	1.35#	(0.84, 2.17)	1.56	n.s.
Employment in high risk occupation and high risk industry:								
Ever/never	1.45	(0.61, 3.44)	.73	n.s.	1.54	(0.96, 2.49)	3.17	n.s.
Smoking standardized	1.54#	(0.59, 4.04)	.77	n.s.	1.32#	(0.78, 2.24)	1.08	n.s.

* n.s. = not significant at the 5% level.
\# Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

employed in a high risk occupation, and the usual employment of case or compeer husband, were evaluated for a potential association with the occurrence of lung cancer (Table 14). More cases (15.9%) than compeers (6.9%) had a family history of lung cancer yielding a significant odds ratio of 2.56 which decreases only slightly (2.37) and remains statistically significant when standardized for smoking status (Appendix C, Table 92) . Only one case and seven compeers with a family history of lung cancer were nonsmokers (smoking-standardized odds ratio = 1.46). A much higher proportion of cases (81.9%) than compeers (68.0%) drank alcohol, resulting in a significant odds ratio of 2.13 which remains the same when age-standardized (Appendix C, Table 93). Standardizing for cigarette smoking, however, yields an odds ratio of 1.05 which is not statistically significant. The majority (80.3%) of cases and compeers had used hair spray while smaller proportions of cases (24.0%) and compeers (20.0%) had used a hand-held hair dryer (Appendix C, Tables 94 and 95). Standardizing for smoking status and use of hair spray or hand-held hair dryer yields odds ratios (0.87 and 1.20, respectively) which are not statistically significant.

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The husbands of cases and compeers most frequently were usually employed in Professional occupations (33.5% and 30.7%, respectively) (Appendix C, Table 96). Frequency distributions of husbands' occupations are similar between cases and compeers except for usual employment in Structural occupations (cases = 24.6%, compeers = 16.5%) for which the

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TABLE 14

SUMMARY OF ODDS RATIO ESTIMATES OF ADDITIONAL VARIABLES CONSIDERED AMONG FEMALE LUNG CANCER CASES AND COMPEERS.

Variables	Odds ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Family history of lung cancer	2.56	1.42	4.60	9.41	< 0.05
Smoking standardized*	2.37	1.23	4.58	6.64	< 0.05
Drank alcohol	2.13	1.41	3.20	13.55	< 0.05
Smoking standardized*	1.05	.65	1.71	.04	n.s.**
Used hair spray	1.00	.65	1.54	.01	n.s.
Smoking standardized*	.87	.53	1.42	.31	n.s.
Used hand-held hair dryer	1.26	.84	1.91	1.21	n.s.
Smoking standardized*	1.20	.77	1.89	.66	n.s.
Husband employed in:					
Structural Occupation	1.65	1.07	2.55	5.22	< 0.05
Smoking standardized*	2.13	1.31	3.47	9.19	< 0.05
Case or compeer not employed in Structural Occupation	1.69	1.09	2.62	5.65	< 0.05
Smoking standardized*	2.22	1.35	3.64	10.02	< 0.05
Construction Industry	2.14	1.33	3.45	10.14	< 0.05
Smoking standardized*	2.77	1.63	4.71	14.30	< 0.05
Case or Compeer not employed in Construction Industry	2.17	1.34	3.51	10.27	< 0.05
Smoking standardized*	2.89	1.69	5.00	14.96	< 0.05
Lived with household member who smoked	1.80	.97	3.34	3.56	n.s.
Smoking standardized*	1.01	.50	2.04	.01	n.s.
Lived with household member who worked in:					
Cement manufacturing	1.94	.80	4.70	1.61	n.s.
Smoking standardized*	3.06	1.11	8.47	4.66	< 0.05
Case or Compeer not employed in Cement Manufacturing	2.21	.88	5.58	2.98	n.s.
Smoking standardized*	3.19	1.15	8.85	4.95	< 0.05
High Rise Construction	2.55	1.30	5.05	6.99	< 0.05
Smoking standardized*	2.57	1.24	5.31	6.49	< 0.05
Case or Compeer not employed in High Rise Construction	2.39	1.20	4.74	6.52	< 0.05
Smoking standardized*	2.41	1.16	5.01	5.52	< 0.05
Insulation Manufacturing (+)	5.52	.64	47.55	1.78	n.s.

* Mantel-Haenszel estimate.
** n.s. = not significant at the 5% level.
(+) All Cases and Compeers who lived with a Household Member who worked in Insulation Manufacturing were smokers. No Case or Compeer who lived with a Household Member who worked in Insulation Manufacturing had worked in Insulation Manufacturing.

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crude odds ratio (1.65) is statistically significant (Appendix C, Table 97). The smoking-standardized odds ratio for husband's usual employment in a Structural occupation (2.13) is slightly higher and also statistically significant. No case and only one compeer whose husband was usually employed in a Structural occupation had also been employed in a Structural occupation and, standardizing for smoking status of cases and compeers, a significant odds ratio of 2.22 is obtained (Appendix C, Table 98). The odds ratio estimate for husband's employment in a Structural occupation among cases and compeers never employed in a Structural occupation is highest (4.64) among cases and compeers who had never smoked cigarettes.

The Manufacturing industry was the most frequent category of usual employment among the husbands of cases (24.4%) and compeers (27.4%) (Appendix C, Table 99). Frequency distributions of the industries in which husband were usually employed differ little except for employment in the Construction industry (cases = 22.4%, compeers = 11.9%; odds ratio = 2.14, statistically significant) (Appendix C, Table 100). The smoking-standardized odds ratio for husband's usual employment in the Construction industry (2.77) is higher and also significant. One case and one compeer whose husband had usually been employed in the Construction industry had also been employed in the Construction industry and the smoking-standardized odds ratio among cases and compeers never employed in the

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Construction Industry is 2.89 which is statistically significant (Appendix C, Table 101). The odds ratio estimate for husband's usual employment in the Construction Industry among cases and compeers never employed in the Construction Industry is highest and statistically significant (6.90) among those who had never smoked cigarettes.

More cases (93.4%) than compeers (88.7%) had lived with a person who smoked cigarettes but the odds ratio (1.01) is not significant when standardized for smoking status of cases and compeers (Appendix C, Table 102). More cases (5.5%) than compeers (2.9%) had lived with a household member who worked in Cement Manufacturing and the crude odds ratio (1.94) is not statistically significant (Appendix C, Table 103). However, the smoking-standardized odds ratio (3.06) among those who had lived with a household member employed in Cement Manufacturing is statistically significant. No case who had lived with a household member employed in Cement Manufacturing had ever been employed in the manufacture of cement, insulation, or asbestos products. One compeer who had lived with a household member employed in Cement Manufacturing had been employed in the Manufacture of Gaskets, Packing, and Sealing Devices. The smoking-standardized odds ratio among cases and compeers never employed in the manufacture of cement, insulation, or asbestos products and who had lived with a household member who worked in Cement Manufacturing is 3.19 which is statistically significant (Appendix C, Table 104). The odds ratio (5.35) is highest and also statistically significant

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among cases and compeers who had never smoked cigarettes, never been employed in the manufacture of cement, insulation, or asbestos products and who had lived with a household member employed in Cement Manufacturing.

Among cases and compeers who had lived with a household member who worked in High Rise Construction the odds ratio is elevated (2.56) and the smoking-standardized odds ratio is also elevated (2.17) and statistically significant (Appendix C, Table 105). Only two cases who had lived with a person employed in High Rise Construction had also been employed in High Rise Construction and the odds ratio (2.39) among cases and compeers who had never been employed in High Rise Construction is statistically significant. Standardizing for smoking status of cases and compeers who had never been employed in High Rise Construction and who had lived with a household member employed in High Rise Construction yields a statistically significant odds ratio of 2.41 which is highest among those who had never smoked (4.24) (Appendix C, Table 106). All cases (n = 5) and compeers (n = 1) who had lived with a household member employed in Insulation Manufacturing were smokers (odds ratio = 5.52, not statistically significant (Appendix C, Table 107). No case or compeer who had lived with a household member employed in Insulation Manufacture had ever been employed in the manufacture of cement, insulation, or asbestos products.

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Histopathologic Cell Types of Carcinoma of the Lung

The 259 women with lung cancer had similar proportions of squamous cell carcinoma (23.6%) and small cell carcinoma (23.9%), while adenocarcinoma comprised the largest proportion of all lung cancer cell types (32.0%) (Appendix C, Table 108). Other cell types are: large cell carcinoma (4.3%), adeno-squamous cell carcinoma (0.8%), carcinosarcoma (0.4%), and fibrous histiocytoma (0.4%). About 15% of the lung cancers were unspecified as to cell type. The majority of lung cancers (80.3%) were confirmed histologically and the remainder were confirmed cytologically (18.0%) or by autopsy (1.6%). Among the three main cell types of lung cancers adenocarcinoma is the predominant cell type among the lung cancers diagnosed histologically and cytologically (37.3% and 45.5%, respectively) while small cell carcinoma is the predominant cell type diagnosed by autopsy (57.1%) (Appendix C, Table 109).

Adenocarcinoma is the most frequent cell type for all age categories, except for 55-59 years (small cell carcinoma) and 70-74 years of age (squamous cell carcinoma). When only the three main cell types of lung cancer are considered, the frequency of squamous cell carcinoma is greatest in ages 70-74 years (54.2%) and 75+ years (40.2%), the frequency of small cell carcinoma is greatest in the 50-54 (40.6%) and 55-59 (40.5%) year age groups, while adenocarcinoma has a high frequency in ages 35-49 (60.0%), 50-54 (43.8%) and 75+ (50.0%) year age groups. The predominant histopathologic cell type of lung cancer among

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smokers is adenocarcinoma (current smokers = 30.3%, exsmokers = 32.3%) and it is also the predominant cell type among the 12 nonsmokers (58.3%) (Appendix C, Table 110). The proportion of squamous cell carcinoma is higher among exsmokers (30.7%) than it is among current smokers (21.1%) while the proportion of small cell carcinoma is higher among current smokers (26.5%) than among exsmokers (19.4%). Adenocarcinoma is the most frequent or one of the most frequent cell types according to category of pack-years of cigarettes smoked, except for 34.22-43.80 pack-years (small cell carcinoma) (Appendix C Table 111).

Summary of Results

The majority of cases (83.0%) and compeers (71.9%) were deceased and, in 1979 the mid-year of the study, almost three fourths of both groups were 50 to 69 years of age. The most frequent usual occupation, determined by longest duration employed of both cases and compeers in all age groups was in the Service category. Most of the occupations in the Service category among both cases (85.1%) and compeers were housewife (92.2%). The largest single industry in which cases (39.2%) and compeers (39.9%) were usually employed was the Service industry. A large proportion of the usual industry category was classified as "unemployed, retired, disabled, or on welfare" (cases = 40.2%, compeers = 50.2%).

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Excessive cigarette smoking is the most outstanding and consistent difference for the women with lung cancer compared to women without the disease. Almost all cases (95.4%) and the majority of compeers (59.7%) had a history of smoking cigarettes. The odds ratio for all smokers compared with those who never smoked cigarettes is 13.89, while it is 15.70 among current smokers and 10.33 among exsmokers. Among women who started to smoke between 6 and 16 years of age, the odds ratio is higher (17.76) than the ratio among those who started to smoke between 21 and 29 years of age (12.90). Study subjects who stopped smoking between 38 to 50 years of age had a much lower odds ratio (4.67) than the ratio among those who stopped smoking at 58 or more years of age (23.33). The highest odds ratio for lung cancer is among women who usually smoked self-rolled cigarettes (33.19) while ratios for filter-tip use (15.44) and nonfilter-tip use (11.54) are lower. A dose-gradient of odds ratios is evident for the usual number of cigarettes smoked per day: 4.67 for less than one pack per day, 11.8 for one pack per day, and 21.2 for more than one pack of cigarettes smoked per day. Similarly, a dose-gradient of odds ratios is evident for duration of having smoked cigarettes: 8.51 for one to 30 years, 14.60 for 31 to 40 years, and 20.00 for having smoked cigarettes for 41 or more years.

Odds ratio estimates for ever employed in a high risk industry or occupation are increased and remain elevated when stratified by frequency, duration, and time-period of

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employment, as well as when stratified by age and/or smoking status. A dose-gradient pattern of smoking-adjusted odds ratios occurs with ever employed in either a high risk industry or a high risk occupation (1.03), a high risk industry (1.07), a high risk occupation (1.21), and both a high risk industry and a high risk occupation (1.34). The smoking-adjusted odds ratio for frequency (1.13) and duration (1.14) of employment in a high risk industry as well as those for frequency (1.24) and duration (1.31) of employment in a high risk occupation are higher than the respective, smoking-adjusted odds ratios for ever employed. A slight dose-gradient is shown in the smoking-adjusted odds ratios for time period of employment in a high risk occupation: employment prior to or during 1969 = 1.14, 1959 = 1.22, 1949 = 1.24. Smoking-adjusted odds ratios for employment in a high risk industry during these same time periods are also elevated but do not reflect a dose-gradient.

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The smoking-adjusted odds ratios for husband's employment in the Construction Industry (2.89) or in a Structural Occupation (2.22) among cases and compeers who, themselves, were not similarly employed are statistically significant. Smoking-adjusted odds ratios are also significantly elevated among cases and compeers who were not employed in, but had a history of having lived with a household member employed in: Insulation Manufacturing (5.52), Cement Manufacturing (3.19) and High Rise

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Construction (2.41).

A family history of lung cancer shows a significant two-fold increase in the smoking-adjusted odds ratio (2.37). A religious preference of Protestant, when compared with a preference of Catholic, has a statistically significant smoking-adjusted odds ratio of 2.13 Cases and compeers who were not married at time of interview, when compared to those who were married, also have a significant smoking-adjusted odds ratio (1.63). No significant increase in smoking-adjusted odds ratio was found for having lived with a household member who smoked cigarettes, the use of hair spray or a hand-held hair dryer, or the consumption of alcohol.

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CHAPTER FIVE

Discussion

In this case-comparison study of the environmental factors related to the risk of lung cancer in women, excessive cigarette smoking is the most outstanding and consistent characteristic evident among the women with lung cancer. Almost all (95.4%) cases smoked cigarettes and the odds ratio estimate among all smokers (13.89) is higher than any previously reported among women and is similar to the highest risk ratio reported among men (13.0*), emphasizing the important role of cigarette smoking in the risk of lung cancer for women as well as for men. The lower odds ratios reported for smoking variables among cohorts in earlier studies of lung cancer among women were probably based on women with a lower lifetime cumulative smoking exposure because of the birth-cohort smoking-effect. The highest odds ratio for lung cancer is among women who usually smoked

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* In studies of lung cancer among men which included more than 5 cases who never smoked. The single exception to this is a study conducted by Koulumies (1953) in Finland in which the odds ratio was 36.0 (USDHHS, 1982).

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self-rolled cigarettes (33.19), a finding which is consistent with that reported by Pickle (1983)+. The gradients of significant odds ratios for number of cigarettes smoked per day, age started smoking, and age stopped smoking cigarettes suggest a strong dose-response effect reported in numerous previous studies of smoking and lung cancer (USDHHS, 1982).

The consistent elevation of risk across all categories of employment in high risk industries and/or high risk occupations, while not statistically significant overall when stratified by smoking and age, is strongly suggestive of the potential role of work-related exposures in increasing the risk of lung cancer in women. This concurs with studies of men employed in specific industries and occupations (Blot et al., 1977; Figueroa et al., 1973; IARC, 1977; Lloyd, 1971; Lundin et al., 1969; Pedersen et al., 1973; Williams et al., 1977).

The higher odds ratio estimates for frequency of employment and duration of employment, while not statistically significant when controlled for smoking, suggest a dose response effect with employment in a high risk industry or employment in a high risk occupation. The increased risk associated with employment in a high risk occupation from 1940 through 1949 is in accordance with the hypothesis that, during and following that period of war, women were employed in high risk occupations. A significant

+ L.W.Pickle. Personal communication, 1983.

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p-value for an extended odds ratio demonstrates the extent to which that odds ratio may be merely a reflection of chance variation. If the p-value is very small then the odds ratio is far enough from unity that the event probably did not occur by chance. Considering the adequate sample sizes analyzed, the consistency of the associations, the biological gradient of increased risk ratios while stratifying the data in various dimensions, and the increased risk associated with employment during an earlier time period it seems unlikely that the associations noted with employment in a high risk industry and/or a high risk occupation and the occurrence of lung cancer could have occurred by chance.

Odds ratios among cases and compeers who smoked cigarettes and who had high risk employment are significantly increased and the proportional increase from employment in either a high risk industry or occupation (9.30) to those employed in both a high risk industry and a high risk occupation (15.74) is 69.3% (Table 15). Odds ratios are consistently higher among cases and compeers who both smoked cigarettes and were employed in a high risk industry and/or occupation than are the odds ratios among cases and compeers who smoked cigarettes but were not employed in high risk areas. The odds ratios among cases and compeers who never smoked cigarettes but had high risk employment are unstable due to the small number of cases employed in a high industry (N = 3) or a high risk

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Table 15

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN HIGH RISK INDUSTRIES AND/OR OCCUPATIONS BY SMOKING STATUS

Smoked cigarettes	High risk employment	Odds ratios for high risk employment in Either an industry or occupation	Industry	Occupation	Both an industry and occupation
YES	YES	9.30	11.01	13.17	15.74
YES	NO	7.91	9.31	9.49	10.53
NO*	YES	0.30	0.41	0.12	0.19
NO	NO	1.00	1.00	1.00	1.00

* The odds ratios for cases and compeers who never smoked cigarettes and had a high risk employment are unstable estimates because of the small number of cases employed in a high risk industry or a high risk occupation who never smoked cigarettes (3 and 0, respectively). See Appendix C, Table 108 for estimates.

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occupation (N = 0). The differences in gradients of odds ratios between the smokers with high risk employment and the smokers who were not employed in these areas need to be examined for patterns of smoking by employment categories.

The direct effect of cigarette smoking on the occurrence of lung cancer continued to be overwhelming when the effects of religious preference and marital status were controlled in the analysis. Marital status may be a reflection of lifestyle associated with different patterns of smoking such as, starting to smoke at an earlier age, smoking a greater number of cigarettes, or never having stopped smoking. Cases who were divorced or separated comprised the greatest difference (7.3%) in marital status within the "not married" group. Nationally, these two groups have the highest rate of smoking among women: divorced = 54.8%, separated = 45.1%, while widows have the lowest (20.4%) (USDHHS, 1979). Higher education status is, perhaps, also associated with earlier age at starting to smoke. The smoking-adjusted odds ratios for religious preference and for marital status were statistically significant and these associations need further investigation for a possible confounding effect. Specifically, a woman's religious preference as a child or her marital status may guide her choice or opportunity of employment as well as affecting her choice of persons with whom she lives, thus influencing her lifestyle and the possibility of either direct or "bystander" exposures.

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Husband's employment in a construction industry or employment in a structural occupation, when controlled for smoking and employment status of cases and compeers, were found to be significant risk factors for lung cancer in women in this study. Having lived with a household member employed in the manufacture of insulation or cement or employed in a high rise construction industry, controlling for smoking and employment status of cases and compeers, also were found to be significant risk factors for lung cancer in women. The increased risk of lung cancer associated with husband's or household member's employment in these industries gives particular credence to the indirect or "bystander" effect reported in previous studies, especially asbestos-related exposures (see literature review). Further investigation of this finding is needed before a more definitive statement can be made concerning the risk of lung cancer among women in Harris county.

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The use of hair spray or a hand-held hair dryer, hypothesized as risk factors for lung cancer, was not substantiated. The use of alcohol, when stratified by smoking status, showed no significant increase in risk of lung cancer. Family history of lung cancer shows about a two-fold increase in the risk of lung cancer which supports the increase in frequency in specific types of cancer among relatives reported previously. It is possible that some environmental and/or behavioral practices in the familial micro-environment affect the risk of lung cancer, such as

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dietary factors or indoor air pollution, which could not be evaluated in this study population.

The predominance of adenocarcinoma among the histopathologic cell types in women with lung cancer as well as the increase in frequency of squamous cell carcinoma with age, the higher frequency of small cell carcinoma in younger age groups, and the predominance of adenocarcinoma in both younger and older age groups has been observed in previous studies (Ives et al., 1983). The number of cases who never smoked cigarettes (12) is small and may not be representative of histopathologic distributions.

Limitations of the study

Most of the nonresponse rate (34.3%) is due to cases and compeers not being located or having a residence outside the study area (54.7%). It is possible the cases and compeers not located were not currently or ever employed, perhaps housewives, and, hence, were less easily found through sources other than friends or relatives. A slightly larger proportion (1.9%) of compeers than cases were not located. If these missing compeers were housewives and not employed in high risk occupations or industries, an underestimate of odds ratio estimates for employment in high risk areas could result because of the inclusion of a higher proportion of compeers with, perhaps, a history of employment in high risk areas. The differential proportion of 1.9%, however, is small and unlikely to have influenced

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results to any significant extent. In addition, similar tracing and follow-up procedures were applied to cases and compeers and it is unlikely any differential response related to locating cases and compeers occurred because of study methods.

The 14.8% overall refusal rate of cases and compeers comprises less than half (43.2%) of the total nonresponse rate. Refusal rates are lower among cases than among compeers, even with the inclusion of physicians' refusals to permit interviews with 10 eligible cases. Occasionally, in case-comparison studies cases may "self-select" out of the study because of the legal, social, or political climate. The lower refusal rate among cases than compeers indicates that no large proportion, if any, cases "self-selected" out of the study. Sometimes, in case-comparison studies, cases or their surrogates are more aware of or have better recall than compeers of potentially hazardous associations between risk factors and disease because of their increased awareness of the disease process. This possible reporting bias could result in higher proportions of employment in high risk occupations and industries being reported among cases and could lead to overestimations of risk for associations between employment and disease. Other than tobacco, asbestos has been the most widely publicized respiratory carcinogen during the past decade and occupations in a shipyard are the most likely to be associated with lung cancer by the general public.

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Employment in the manufacture of industrial organic chemicals, the construction industry, or in occupations in the mining and refining of metal compounds of arsenic, nickel, or chromium are less likely to be known by the general public as having an association with lung cancer. Furthermore, there is little specific data available on the health effects of a given occupational or industrial exposure among women. Consequently, it is unlikely that cases or their next-of-kin overreported employment in high risk occupations or industries because of an awareness of potential causes of lung cancer.

The ascertainment or selection of compeers can influence study results significantly and may lead to incorrect conclusions. The use of vital status as a matching criterion may bias study results (Gordis, 1982). Decedent compeers, for instance, may have had a lifestyle pattern different from that of living compeers and this could have influenced their health status. Decedent compeers, for example, may have smoked more and smoked longer than living compeers and may have died from a smoking-related disease. The odds ratios for smoking status would then be lower than would have been estimated if the compeers had been representative of the living population. Odds ratios for smoking status are considerably higher among living than deceased cases and compeers which illustrates the effect of this bias. Study results may also be affected by the inadvertent inclusion of compeers with a diagnosis of lung cancer would decrease odds ratio estimates. Questionable

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diagnoses of deceased compeers, however, were carefully checked with death certificates to avoid this possibility. The selection of living compeers 65 or more years of age from Medicare records is unlikely to have influenced employment patterns inasmuch as their eligibility for Medicare requires only that they be 65 or more years of age. Living compeers chosen from records of the Texas Department of Public Safety had acquired a license to drive an automobile. A slightly lower percentage (6.3) of compeers than cases had a current driver's license which may be a reflection of the proportion of older housewives who did not require a license because of earlier lifestyles. If housewives were less likely to have been employed in a high risk occupation or industry and if there is an excess of housewives among the cases because the selection of compeers from driver's license records favored exclusion of housewives, then odds ratios for employment in high risk areas would be under-estimated. The 1.3% higher proportion of widows among living cases than living compeers supports the possibility of this selection bias but the difference is slight and unlikely to have affected results to any great extent. The usual occupations of cases and compeers determined by longest duration employed reveal a 5.2% greater proportion of housewives among living cases than living compeers but usual occupations reported by respondents show 8.0% more living compeers than living cases whose usual occupation was housewife. It is not clear,

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therefore, if the possible selection of living compeers from records of the Texas Department of Public Safety had any effect on employment patterns found among compeers.

The higher proportion (12.4%) of next-of-kin interviews completed among cases than among compeers combined with the possibility that next-of-kin have limited employment history information, especially employments 30 or 40 years ago during 1940 to 1950, could result in greater under-reporting of high risk employments for cases than for compeers. This greater reporting difference among cases than among compeers could lead to underestimates of risk for employment (ever versus never) in high risk industries or high risk occupations. On the other hand the next-of-kin of deceased cases might have been more zealous, perhaps because of greater familial interest in cause-and-effect associations, than the next-of-kin of deceased compeers and this could lead to over-estimates of risk for employment in a high risk industry or occupation. The next-of-kin of both cases and compeers consistently reported lower proportions of high risk employments than were reported by living cases and compeers. The most likely effect, if any, on risk estimates for employment in a high risk industry or a high risk occupation resulting from the higher proportion of interviews completed with the next-of-kin of cases than with the next-of-kin of compeers is that of under-estimation of risks.

The greater reporting differential of employment (ever versus never) in high risk industries and high risk

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occupations by vital status among the compeers than among the cases could have contributed also to the lower odds ratio estimates among the living than deceased cases and compeers. Living compeers reported higher proportions of high risk employments than were reported by the next-of-kin of compeers (industry = 9.2%, occupation = 6.0%). Similarly, living cases reported higher proportions of high risk employments than were reported by the next-of-kin of cases but the differences are slightly smaller (industry = 4.2%, occupation = 4.3%) than the differnces among the compeers. These higher proportional differences of high risk employments reported by vital status among compeers than among cases could have contributed to the lower odds ratios among the living than deceased cases and compeers. On the other hand, the lower odds ratio estimates among living than deceased cases and compeers for high risk employments could be reflecting true differences in employment by vital status in that more living compeers than deceased compeers and/or fewer living cases than deceased cases were employed in high risk industries or occupations.

The objective of the current analysis is concerned with occupations and industries classified as two single high risk groups rather than specific industries or occupations. Analysis of the two groups of high risk industries and high risk occupations represents a summary approach to identification of risks. Subsets of high risk occupations or industries may be highly associated with lung

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cancer but the small numbers of women employed in such categories were too few for appropriate analysis, for example, only three cases and no compeers had a usual employment in the Mining industry. The study of health hazards in specific industries or occupations is more accurately accomplished when groups are large and can represent trends more reliably than is possible with three or four individuals. Results of the analysis of large groups of industries or occupations, however, may reflect a dilution effect from low risk employments included with high risk employments. In order to avoid a dilution effect, the classification of occupations and industries into risk categories is of paramount importance. Classification of industries and occupations into high risk was based on findings in the literature which indicated a recognized or possible association between employment and the occurrence of lung cancer. Some studies on which the classification was based reported inconclusive findings and this could lead to incorrect inclusion of low risk employments with high risk employments. Since classification was conducted a priori and was applied similarly to cases and compeers, any misclassification which occurred would have affected both groups in a nondifferential manner. All occupations were coded using a classification which permits identification of specific tasks in relation to data, people, and things and facilitated determination of occupations associated with exposures possibly related to lung cancer. The industrial coding classification is specific to subcategories which

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identify product manufacturing and, thus, permits differentiation of similar but different industries such as, contractors for structural steel erection or wrecking and demolition work.

Although cases and compeers were employed in high risk industries such as, Construction; Manufacturing Furniture and Fixtures, Paper, Synthetic Rubber, Petroleum, Tires, or Steel; Laundry and Dry Cleaning Services; and Automotive Repair Shops, none of them had been employed in other industries possibly associated with lung cancer such as, Manufacturing Industrial Organic Chemicals (Bis(chloromethyl) ether, Isopropyl alcohol); Mining of Metals, Anthracite, Bituminous Coal and Lignite; or the Primary Smelting and Refining of Nonferrous Metals such as cadmium, chromium, and nickel. Similarly, even though cases and compeers were employed in potentially high risk occupations such as, Cosmetologist, Cook, Rubber Tester, Tool Grinder, Painter, Welder, Shipfitter, and Laboratory Tester, none of them had been employed in other occupations possibly associated with the occurrence of lung cancer such as, occupations in the Processing of Paper, Petroleum, Coal, or Leather; Excavating, Grading, and Paving Occupations; and Occupations in the Extraction of Minerals. This dearth of women employed in industries that thrive on the abundance and natural resources of Texas, such as, mining, petroleum and coal, agriculture, construction, and aircraft has also been observed by England et al. (1978).

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The ascertainment of women with lung cancer diagnosed during 1977 to 1980 permitted an examination of the effects of employment during World War II when hazardous work exposures were more likely to resemble those of men. If the latency period for lung cancer is assumed to be 30 years, then this is an appropriate time to investigate the effects of employment patterns of women in the 1940's and 1950's. If, however, the latency period for lung cancer is either shorter (such as occurred with workers exposed to BCME) or longer than 30 years (such as exposure to asbestos) other studies would be more informative. The slight increase in risk of lung cancer noted among women with lung cancer who were employed in high risk occupations or industries from 1940 to 1949, 1959, or 1969 may be relatively small because of: 1) the small numbers of women ever employed in high risk industries or occupations during these periods of time, 2) the short duration of their employment, or 3) the latency effect discussed above.

Most studies of associations between exposures at work and the occurrence of lung cancer have been conducted among men and it is possible that women have different types or levels of susceptibility than men when exposed to hazardous substances in the work place (Kotin, 1968; Messite and Bond, 1980). Although women were employed in a high risk occupation or industry they may not have been exposed to hazardous substances or, if exposed, they may not have experienced the amount or type of exposures that men have experienced in the past. Women employed in high risk areas

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may have practiced healthy personal habits such as a strong emphasis on cleanliness and consistent use of protective equipment and, thus, reduced their risk of disease. More likely these differences reflect exposure differences. Clearly, the pattern in women associated with smoking exposures is beginning to parallel that observed in males and it is suggested here that the same may be true for workplace exposures if women were employed for the same frequency and duration periods as were men.

Since most cases were deceased (83%), it is possible that a higher proportion of husbands of cases than of compeers reported their own usual occupation and industry which could result in more accurate reporting of high risk occupations and industries among the cases. The difference in the proportion of widowed cases (29.0%) and widowed compeers (26.0%), however, is small and the effect, if any, on frequency distributions of husband's usual employment would be slight.

The possibility of double reporting of husband and household member employed in high risk industries was investigated. Among those cases and compeers who had lived with a household member employed in Cement Manufacturing, no husband had been reported as having been usually employed in this industry. Similarly, no husband was reported as having a usual employment in High Rise Construction among the cases and compeers who had lived with a household member employed in that industry. Therefore, it was clear to the respondent

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that household member and husband were separate persons.

A family history of lung cancer might be more frequently reported among cases than compeers because of a possible interest in the familial aspects of the disease. It is unlikely that healthy compeers or the next-of-kin of a compeer who died of a non-malignant disease would have discussed the occurrence of lung cancer in the family to the extent that cases or their next-of-kin would have explored it. It is not possible in this study to investigate a possible difference in the reporting of family history.

In summary, the major limitations of the study are the 1) the absence of women employed in some major high risk industries and occupations which limits the evaluation of risk associated with possible high risk employments , 2) the small numbers of women employed in specific high risk industries and occupations thus restricting analysis to large groups of high risk industries and occupations, and 3) an average duration of employment less than 11 years which may be insufficient exposure time for some carcinogens to have an effect. Risks for employment in a high risk industry or a high risk occupation may be under-estimated because of a larger proportion of deceased cases than deceased compeers in the study resulting in an under-reporting of high risk employments, particularly those employments during World War II.

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Summary:

The overwhelming contribution of cigarette smoking to the risk of lung cancer in women is clearly documented. It is also clear that women have at least equal risk of developing lung cancer from smoking cigarettes as studies among men have demonstrated since the 1950's. The decrease in odds ratios among women who stopped smoking between 38 years to 50 years of age (4.7) compared with those who stopped smoking at 58 or more years of age (23.3) is evidence of the benefits of discontinuing smoking cigarettes at an early age.

Women's employment in a high risk industry or a high risk occupation results in consistently increased smoking-adjusted odds ratios with the frequency and duration of employment demonstrating a moderate dose-response effect. The moderate increase in risk of lung cancer associated with women's employment in a high risk industry or a high risk occupation occurred although the average duration of employment did not exceed 11 years and some documented high risk industries and high risk occupations were not represented. These results indicate that, similar to their response to cigarette smoking, women as well as men may have an increased risk of lung cancer associated with employment in a high risk industry or a high risk occupation.

The odds ratios for lung cancer among women whose husband or a household member was employed in a Structural Occupation or in the Cement Manufacturing, Insulation

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Manufacturing, or Construction Industries are unusually high, perhaps due to hazardous exposures which were intense, of long duration, or during a period of high susceptibility.

The results suggest that familial and sociologic factors, such as family history of lung cancer, marital status, religious preference, and educational status, may influence the risk of lung cancer, perhaps by establishing patterns of behavior which affect the development disease or lifestyles associated with increased exposure to cigarette smoking. The lack of increased risk of lung cancer found with case and compeer exposure to a household member's cigarette smoking as well as with the use of hair spray, a hand-held hair dryer, or alcohol indicates these are not major factors associated with the occurrence of lung cancer in women. The risk, however, may vary with the amount and intensity of exposure to these variables.

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Recommendations:

There is substantial evidence of a strong association between cigarette smoking and the occurence of lung cancer in women as well as men. Efforts should be directed toward initiating and supporting activities focused on preventing people, particularly children and adolescents, from starting to smoke. In addition, activities concerned with encouraging and supporting smokers to stop smoking should be promoted and strengthened.

The specific industries and occupations associated

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with an increased risk of lung cancer need to be identified in order to alert authorities and workers of potential hazards so they can strengthen and initiate preventive measures.

Greater emphasis should be placed on the sociologic and familial aspects of the disease process with consideration of major factors which characterize the lifestyle of persons who develop lung cancer.

More specific investigations of indirect or "bystander" exposures on the occurence of disease need to be conducted, including investigations of both lung cancer and other respiratory illnesses.

Careful attention should be given to matching comparison subjects on the basis of vital status. At the time the study was designed, this issue was debated but unresolved among epidemiologists.

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APPENDIX A

Summary of Findings in the Literature

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APPENDIX A TABLE 1

STUDIES OF LUNG CANCER IN WOMEN PUBLISHED SINCE 1950 WITH SELECTED VARIABLES REPORTED

	Authors, source, year published	Time of study	Location of study	No. of cases Male	No. of cases Female	Primary cases specified	Histology Confirmed	Comparison subjects	Source(s) of information: method of data collection	Variables reported: Smoking	Occupation of women	Residence	Education	Marital	Other
1.	Wynder & Graham, JAMA, 1950	Not stated	Variety of hospitals in 11 States	644	40	No	Yes	General hospital population	Cases: interviewed (93%), mailed quest.(5%) Friend: interviewed(2.5%)	Yes	No	No	No	No	Age
2.	Doll & Hill, Br Med J,1952	1948-1952	Hospitals in England	1357	108			Hospital patients, diag. other than cancer or chest disease	Cases: interviewed Comparison subjects: interviewed Age, race matched	Yes	"No gross association with an occupation".	Yes	No	No	SES Age
3.	Breslow et al., AJPH, 1954	1949-1952	Hospitals (11 in California	493	25	No	Yes	Hospital patients, diag. other than cancer or chest disease	Cases: interviewed Comparison subjects: interviewed Age, race matched	Yes	No	No	No	No	Age
4.	Wynder et al., NEJM, 1956	1953-1955	Patients from 11 hospitals (N.Y., Mass.) admitted to Memorial Cent. Cancer & Allied Dis.	-	196	No	Yes	hospital patients with cancer or benign tumors other than resp. or upper G.I.	Cases:interviewed (24%), Friends; question (30%), Cases with no interview or question (46%) Comparison subjects: interviewed (100%)	Yes	Housewife, White collar, Domestic, "No difference of any consequence"	Yes	Yes	No	Age, prev. lung disease
5.	Haenszel et al., JNCI, 1958	1955-1957	Institutions (29) in 24 cities in U.S.A.	-	158	prim.= 89%, metast.= 11%	Yes	Same instit. as case; 2/case	Cases: interviewed (100%) Comparison subjects: interviewed (100%) Age matched	Yes	White collar, Nonwhite collar."No significant results".	No	No	"No sig. results"	Age, race

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APPENDIX A TABLE 1

STUDIES OF LUNG CANCER IN WOMEN PUBLISHED SINCE 1950 WITH SELECTED VARIABLES REPORTED

	Time of study	Location of study	No. of cases Male	No. of cases female	Primary cases specified	Histology Confirmed	Comparison subjects	Source(s) of information: method of data collection	Variables reported: Smoking	Occupation of women	Residence	Education	Marital	Other
6. Boucot & Perry, Dis Chest, 1960	1948-1955	Hospitals (39) in Philadelphia	-	138	74%	74%	Males	Hospital records primarily	No	No	No	No	No	Age, race prev, resp, dis
7. Hanbury, Thorax, 1964	1948-1959	Hospital in London	-	100	No	Yes	None	Hospital records	Yes	"Nothing significant"	Yes	No	Yes	Age, prev, resp, dis Family hx
8. Haenszel & Taeuber, JNCI, 1964	1958-1959	Current Mort. Sample (10% deaths in U.S.A.)(CMS)	-	513	No	Yes	Current Pop. Survey & CMS with diag. of cancer of colon & rect. Sex matched	Family informants, physicians; questionnaire	Yes	No	Yes	No	No	Birth-place, Nativity
9. Vincent et al., Cancer, 1965	1947-1963	Hospital in St. Louis, Missouri	-	163	Yes	Yes	Male surgical series	Medical records, Physicians; questionnaire Relatives: telephone	Yes	"Nearly all were housewives"	Yes	No	No	Age, race
10. Hammond, NCI Monogr, 1966	1959-1963	Counties in 25 States	1159	210	Mixed	No	None	Volunteers; questionnaire Death certificates, Physicians	Yes	No				Age
11. Lombard & Huyck, Growth, 1968	1960's	Patients in Massachusetts	-	225	No	Yes	Volunteers	Cases: medical records/ interview Comparison subjects: interviewed	Yes	10 cases described	Yes	No	Yes	Age, hysterectomy, resp. dis, family hx
	1952-1962	Massachusetts	-	540	No	No	None	Relatives, friends: questionnaire Death records	Yes	No	No	No	No	

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APPENDIX A TABLE 1

STUDIES OF LUNG CANCER IN WOMEN PUBLISHED SINCE 1950 WITH SELECTED VARIABLES REPORTED

	Authors, source, year published	Time of study	Location of study	No. of cases Male	No. of cases Female	Primary cases specified	Histology confirmed	Comparison subjects	Source(s) of information; method of data collection	Variables reported: Smoking	Occupation of women	Residence	Education	Marital	Other
12.	Cooper et al., Arch Environ Hlth 1968	1957-1963	Hospitals (12) in Philadelphia	1250	122	Yes	Yes	None	Medical records and interview	Yes	No	No	No	No	Age
13.	Ashley & Davies, Thorax, 1969	"past 15 years"	Hospitals in Wales	-	83	No	67%	Males	Hospital records	Yes	No	No	No	No	Age
14.	Deaner & Trummer, J thorac Cardio Surg 1970	1962-1967	Naval hospital in San Diego		68	Yes	Yes	None	Hospital records	Yes	Naval personnel	No	No	No	
15.	Wynder et a ., JAMA, 1970	1966-1969	Memorial Sloan Kettering Cancer Cent.,N.Y.	284	66	No	Yes	Same instit., no known tobacco related disease, Age, sex matched (2/ case)	Cases; interviewed Comparison subjects; interviewed	Yes	No	No	No	No	Age, religion
16.	Wynder et al., JNCI, 1973	1970-1972	Hospitals (7) in N.Y., California, Texas	-	116	No	Yes	Same instit., no known tobacco related disease, Age,race,sex matched (4/ case)	Cases; interviewed Comparison subjects; interviewed	Yes	White collar, Blue collar, "No significant difference"	Yes	Yes	No	Age, religion
17.	Kennedy, Thorax, 1973	1955-1971	Hospitals in England	-	168	No	Yes	None	Hospital records	Yes	No	No	No	No	

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APPENDIX A TABLE 1

STUDIES OF LUNG CANCER IN WOMEN PUBLISHED SINCE 1950 WITH SELECTED VARIABLES REPORTED

Authors, source, year published	Time of study	Location of study	No. of cases Male	No. of cases Female	Primary cases specified	Histology Confirmed	Comparison subjects	Source(s) of information; method of data collection	Variables reported: Smoking	Occupation of women	Residence	Education	Marital	Other
18. Beamis et al., Med Clin NA, 1975	1957-1972	Lahey Clinic Foundation	-	230	Yes	87%	None	Hospital records	Yes	In home/outside home	Yes	No	No	
19. Garfinkel et al., JNCI, 1977	1958-1962	Alameda County, Calif	-	176	No	No	Computer file recorded deaths.	Computer file of recorded deaths, Age, race, date of death matched	No	Beauticians/ Non-Beauticians	Yes	No	No	Race
20. Vincent et al., Cancer, 1977	1962-1975	Roswell Park Memorial Inst Buffalo, N.Y.	1404	278	Yes	Yes	Hospital patients	Cases: interviewed Comparison subjects: interviewed	Yes	No	No	No	No	
21. MacLennan et al., JNCI, 1977	1972-1973	Hospitals (3) in Singapore	147	86	No	50%	Same hospit., excluded selected dis. Age, dialect matched (2/case)	Female cases: interviewed (69%). Comparison subj.: interviewed (7%). Hospital records	Yes	Rubber packing (N=1)	Yes	Yes	Yes	Incense, paying patients, car, own house
22. Williams et al., JNCI, 1977	1969-1971	Third National Cancer Survey	432	128	No	95%	"Inter-cancer" comparison with INCS; census popul.	Cases, spouse, offspring, others; interviewed (53%)	Yes	Relative odds for occup.& industries	Controlled in analyses		No	Alcohol
23. Hanck et al., JNCI, 1977	1972-1975	Canc. Surveillance Prog. Los Angeles County, Calif.	3496	1858	No	No	None	Hospital records	Yes	Ratio estimates (PIR, SIR) for 14 occupational categories	No	No	No	
24. Hinds et al., Int J Cancer 1981	1968-1978	Hawaii Tumor Registry	-	291	No	Yes	Sample from Health Surveillance Program, Sex, race matched	Cases: medical records Comparison subjects: interviewed	Yes	No	Yes	S.E. index	No	Socio-economic index

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APPENDIX A TABLE 2

PERCENTAGE OF SMOKERS AMONG WOMEN WITH LUNG CANCER IN SELECTED STUDIES

Author(s), date published, (time period covered)	Total number of cases	Smoking history unknown No.	Smoking history unknown %	Smokers among those known %	Source(s) of information on smoking status
United States and Europe:					
1. Doll & Hill, 1952, (1948-52)	108			63.0	Case interview.
2. Haenszel et al., 1958, (1955-57)	158	1	.6	48.4	Case interview.
3. Haenszel & Taeuber, 1964, (1958-59)	749			39.1	Family, physicians
4. Vincent et al., 1965, (1947-63)	163	5	3.1	32.3	Records, relatives, physicians.
5. Hammond, 1966, (1959-63)	183			44.3	Questionnaire.
6. Lombard & Huyck, 1968, (1952-33)	112			33.6	Relatives or friends interview.
(1959-62)	428			45.1	
7. Ashley & Davies, 1969, (1954-68)	83	27	32.5	58.9	Records.
8. Deaner & Trummer, 1970, (1962-67)	68			91.2	Records.
9. Wynder et al., 1970, (1966-69)	66			69.7	Case interview.
10. Wynder et al., 1973 (1970-72)	108			84.2	Case interview.
11. Kennedy, 1973, (1955-71)	168	56	33.3	71.4	Records.
12. Beemis et al., 1975, (1957-72)	230	88	38.3	57.8	Records.
13. Harley, 1976, (1964-68)	132	16	13.8	77.6	Not stated.
14. Vincent et al., 1977, (1962-75)	278	77	28.0	81.1	Case interview.
Primarily Oriental origin:					
15. Murakami, 1975, (1962-73)	59	19	32.2	22.5	Records.
16. Leung, 1977, *(not stated)*	80			56.3	Not stated.
17. MacLennan et al.,1977. (1972-73) Cantonese	39			53.8	Case interview.
non-Cantonese	47			51.1	Case interview
18. Colbourne & Ho, 1978, (1976-77)	111			55.9	Case interview.
19. Hinds et al., 1981, (1968-78) Japanese	176	50	28.4	54.1	Records.
Chinese	57	18	26.9	77.6	Records.
Hawaiian	132	16	13.8	25.0	Records.

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APPENDIX B

Study Methods: Lists and Records

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APPENDIX B TABLE 1

DISEASES OR CAUSES OF DEATH WHICH EXCLUDED POTENTIAL COMPEERS FROM THE STUDY*

Disease or cause of death which excluded potential compeers from the study	International Classification of Diseases (ICD) Code (1977) *
Tuberculosis	010x - 018x
Nasopharyngeal cancer	147x. 149x
Esophageal cancer	150x
Laryngeal cancer	161x
Lung cancer	162x - 165x. 231x
Chronic bronchitis	491x
Emphysema **	492.
Bronchial asthma +	493x
Chronic obstructive pulmonary disease (COPD) other than chronic bronchitis or emphysema	490.. 494.. 495x. 496.
Anthracosilicosis	500.
Asbestosis	501.
Silicosis	502.
Pneumoconiosis **, Byssinosis +	503.. 504.
Homicides**	E950x
Suicides**	E960x

* Potential compeers for whom the medical history section of the interview or the diagnosis on the mortality tape from the Texas State Department of Health indicated that they had had one or more of the diseases listed were excluded from the study. Death certificates of decedent compeers whose next-of-kin reported them as having had one or more of the excludable diseases were also reviewed. Those compeers whose underlying cause of death on the death certificate was attributed to an excludable disease were removed from the study.

* The use of 3 digits followed by an "x", e.g. 010x indicates that all subcategories are also excluded.

**Decedent compeers only.

+ Living compeers only.

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APPENDIX B TABLE 1

TELEPHONE VALIDATION OF THREE QUESTIONS ON PATTERNS OF SMOKING WHICH WERE ASKED OF 70 CASES OR CONTROLS DURING THE PERSONAL HOME INTERVIEW

Question	Total No.	Total %	Answer during telephone interview was the same. No.	Same %	Greater No.	Greater %	Smaller No.	Smaller %	Don't know* No.	Don't know* %
1. Number of cigarettes/day	70	100.0	44	62.9	12	17.1	10	14.3	4	5.7
2. Age started. difference in number of years	70	100.0	29	41.4	18	25.7	17	24.3	5	8.6
3. Age stopped. difference in number of years	70	100.0	51	72.9	9	12.9	8	11.4	2	2.9

Question 1. Over the years, about how many cigarettes or packs of cigarettes have you smoked a day?

Question 2. At what age did you start smoking cigarettes?

Question 3. At what age did you stop smoking cigarettes?

* Don't know: a response of 'don't know' was given in either the personal or telephone interview while a specific number was given in the other interview.

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APPENDIX B, TABLE 3

INDUSTRIES SELECTED AS HIGH RISK FROM A COMBINED FREQUENCY DISTRIBUTION OF INDUSTRIES OF CASES AND COMPARISON SUBJECTS.

CATEGORY OF "HIGH RISK" INDUSTRY	CODE NUMBER (SIC*)
MINING	
Oil and gas extraction	1300
Crude petroleum and natural gas	1311
Drilling oil and gas wells	1381
Oil and gas field exploration services	1382
CONSTRUCTION	
Building construction-general contractors and operative builders	1500
General contractors-single family houses	1521
General contractors-residential buildings, other than family	1522
General contractors-nonresidential buildings	1540
General contractors-industrial buildings and warehouses	1541
General contractors-nonresidential buildings, other than industrial buildings and warehouses	1542
Construction other than building construction - general contractors	1600
Heavy construction, except highway and street construction	1620
Water, sewer, pipeline, communication and power line construction	1623
Heavy construction, n.e.c.	1629
Plumbing, heating, (except electric), and air conditioning	1711
Masonary, stone setting, and other stonework	1741
Water well drilling	1781
Structural steel erection	1791
Special trade contractors, n.e.c.	1799
MANUFACTURING: FOOD AND KINDRED PRODUCTS	
Food and kindred products	2000
Meat packing plants	2011
Dairy products	2020
Canned fruits, vegetables, preserves, jams, and jellies	2033
Rice milling	2044
Bread and other bakery products, except cookies and crackers	2051
Cookies and crackers	2052
Sugar and confectionery products	2060
Candy and other confectionery products	2065
Beverages	2080
Malt beverages	2082
Fresh or frozen packaged fish and seafoods	2092
Roasted coffee	2095
Food preparations, n.e.c.	2099
MANUFACTURING: TOBACCO MANUFACTURERS	
Cigarettes	2111

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APPENDIX B, TABLE 3 (continued)

CATEGORY OF "HIGH RISK" INDUSTRY	CODE NUMBER (SIC*)
MANUFACTURING: TEXTILE MILL PRODUCTS	
Textile mill products	2200
Knitting mills	2250
Thread mills	2284
Lace goods	2292
Textile goods, n.e.c.	2299
MANUFACTURING: APPAREL AND OTHER FINISHED PRODUCTS MADE FROM FABRICS AND OTHER SIMILAR MATERIALS	
Apparel and other finished products made from fabrics and other similar materials	2300
Men's, youths', and boys' furnishings, work clothing, and allied garment	2320
Men's youths', and boys' shirts (except work shirts) and nightwear	2321
Women's, misses', and juniors' dresses	2335
Hats and caps, except millinery	2352
Miscellaneous fabricated textile products	2390
Textile bags	2393
MANUFACTURING: LUMBER AND OTHER PRODUCTS, EXCEPT FURNITURE	
Sawmills and planing mills, general	2421
Wood kitchen cabinets	2434
Wood preserving	2491
MANUFACTURING: FURNITURE AND FIXTURES	
Wood household furniture, except upholstered	2511
Mattresses and bedsprings	2515
Office furniture	2520
Drapery hardware and window blinds and shades	2591
MANUFACTURING: PAPER AND ALLIED PRODUCTS	
Paper and allied products	2600
Die-cut paper and paperboard and cardboard	2645
Converted paper and paper board products, n.e.c.	2649
MANUFACTURING: PRINTING, PUBLISHING, AND ALLIED PRODUCTS	
Printing, publishing, and allied industries	2700
Newspapers: publishing, publishing and printing	2711
Periodicals: publishing, publishing and printing	2721
Books: publishing, publishing and printing	2731
Commercial printing	2750
Commercial printing, lithographic	2752
Engraving and plate printing	2753
MANUFACTURING: CHEMICALS AND ALLIED PRODUCTS	
Chemicals and allied products	2800
Industrial inorganic chemicals, n.e.c.	2819
Synthetic rubber (Vulcanizable elastomers)	2822
Drugs	2830
Agricultural chemicals	2870

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APPENDIX B, TABLE 3 (continued)

CATEGORY OF "HIGH RISK" INDUSTRY	CODE NUMBER (SIC*)
MANUFACTURING: PETROLEUM REFINING AND RELATED INDUSTRIES	
Petroleum refining and related industries	2900
Petroleum refining	2911
Petro-chemical industries**	2928
MANUFACTURING: RUBBER AND MISCELLANEOUS PLASTICS PRODUCTS	
Tires and inner tubes	3011
Miscellaneous plastics products	3079
MANUFACTURING: LEATHER AND LEATHER PRODUCTS	
Luggage	3161
MANUFACTURING: STONE, CLAY, GLASS, AND CONCRETE PRODUCTS	
Pressed and blown glass and glassware, n.e.c.	3229
Pottery products, n.e.c.	3269
Abrasive, asbestos, and miscellaneous, nonmetallic mineral products	3290
Asbestos products	3292
Gaskets, packing, and sealing devices	3293
MANUFACTURING: PRIMARY METAL INDUSTRIES	
Primary metal industries	3300
Blast furnaces, steel works, and rolling and finishing mills	3310
Blast furnaces (including coke ovens), steel works, and rolling mills	3312
Steel pipe and tubes	3317
Gray iron foundries	3321
Secondary smelting and refining of nonferrous metals	3341
MANUFACTURING: FABRICATED METAL PRODUCTS, EXCEPT MACHINERY AND TRANSPORTATION EQUIPMENT	
Fabricated metal products, except machinery and transportation equipment	3400
Metal cans	3411
Fabricated structural metal products	3440
Metal doors, sash, frames, molding, and trim	3442
Fabricated plate work (boiler shops)	3443
Sheet metal work	3444
Architectural and ornamental metal work	3446
Bolts, nuts, screws, rivets, and washers	3452
Electroplating, plating, polishing, anodizing and coloring	3471
Ordnance and accessories, except vehicles and guided missiles	3480
Small arms	3484
Fabricated metal products, n.e.c.	3499
MANUFACTURING: MACHINERY, EXCEPT ELECTRICAL	
Machinery, except electrical	3500
Construction, mining, and materials handling machinery and equipment	3530
Oil field machinery and equipment	3533

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APPENDIX B, TABLE 3 (continued)

CATEGORY OF "HIGH RISK" INDUSTRY	CODE NUMBER (SIC*)
MANUFACTURING: MACHINERY, EXCEPT ELECTRICAL, continued	
Industrial trucks, tractors, trailers, and stackers	3537
Metalworking machinery and equipment	3540
Commercial laundry, drycleaning, and pressing machines	3582
Air conditioning and warm air heating equipment and commercial and industrial refrigeration equipment	3585
Carbureters, pistons, piston rings and valves	3592
MANUFACTURING: ELECTRICAL AND ELECTRONIC MACHINERY, EQUIPMENT AND SUPPLIES	
Electrical and electronic machinery, equipment and supplies	3600
Power, distribution, and specialty transformers	3612
Motors and generators	3621
Household laundry equipment	3633
Radio and television receiving sets, except communication types	3651
Telephone and telegraph apparatus	3661
MANUFACTURING: TRANSPORTATION EQUIPMENT	
Transportation equipment	3700
Motor vehicles and passenger car bodies	3711
Aircraft and parts	3720
Aircraft	3721
Aircraft parts and auxiliary equipment, n.e.c.	3728
Ship building and repairing	3731
Railroad equipment	3743
Guided missiles and space vehicles and parts	3760
MANUFACTURING: MEASURING, ANALYZING, AND CONTROLLING INSTRUMENTS, PHOTOGRAPHIC, MEDICAL, AND OPTICAL GOODS; WATCHES AND CLOCKS	
Measuring, analyzing, and controlling instruments, photographic medical, and optical goods; watches and clocks	3800
Engineering, laboratory, scientific, and research instruments and associated equipment	3811
Photographic equipment and supplies	3861
Watches, clocks, clockwork operated devices, and parts	3873
MISCELLANEOUS MANUFACTURING INDUSTRIES	
Sporting and athletic goods, n.e.c.	3949
EATING AND DRINKING PLACES	
Eating and drinking places	5810
Eating places	5812
Drinking places (alcoholic beverages)	5813
PERSONAL SERVICES	
Laundry, cleaning, and garment services	7210
Power laundries, family and commercial	7211
Garment pressing, and agents for laundries and dry cleaners	7212

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APPENDIX B, TABLE 3 (continued)

CATEGORY OF "HIGH RISK" INDUSTRY	CODE NUMBER (SIC*)
PERSONAL SERVICES, continued	
Coin-operated laundries and dry cleaning	7215
Dry cleaning plants except rug cleaning	7216
Laundry and garment services, n.e.c.	7219
Photographic studios, portrait	7221
Beauty shops	7231
Barber shops	7241
Funeral service and crematories	7261
Miscellaneous personal services	7299
BUSINESS SERVICES	
Disinfecting and exterminating services	7342
Cleaning and maintenance services to dwellings and other buildings, n.e.c.	7349
AUTOMOTIVE REPAIR, SERVICES, AND GARAGES	
General automotive repair shops	7538
Automotive repair shops, n.e.c.	7539
MISCELLANEOUS REPAIR SERVICES	
Refrigeration and air conditioning service and repair shops	7623
Reupholstery and furniture repair	7641
Repair shops and related services, n.e.c.	7699
NATIONAL SECURITY AND INTERNATIONAL AFFAIRS	
National security	9711
International affairs	9721

*Standard Industrial Classification Manual (1972).

**Special code to encompass industries that could not be coded 2800 or 2900.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX B, TABLE 4

OCCUPATIONS SELECTED AS "HIGH RISK" FROM A COMBINED FREQUENCY DISTRIBUTION OF OCCUPATIONS OF CASES AND AND COMPARISON SUBJECTS.

CATEGORY OF "HIGH RISK" OCCUPATION	CODE NUMBER (DOT*)
MEDICINE AND HEALTH:	
Nurse, instructor	075.121-010
Nurse, head	075.127-018
Nurse, supervisor	075.127-022
Nurse, supervisor	075.137-022
Nurse, office	075.374-014
Nurse, private duty	075.374-018
Nurse, occupational health	075.374-022
Dietitian, chief	077.117-010
Dietitian, technician	077.121-010
Dietitian, clinical	077.127-014
Dietitian, consultant	077.127-018
Medical-laboratory technician	078.381-014
Medical assistant	079.367-010
Medical-service technician	079.367-018
Dental assistant	079.371-010
Nurse, licensed practical	079.374-014
Surgical technician	079.374-022
Nurse, practical	354.374-010
Psychiatric aide	355.377-014
Nurse aide	355.674-014
Food service worker, hospital	355.677-010
BARBERING, COSMETOLOGY, AND RELATED:	
Manager, beauty shop	187.167-058
Barber	330.371-010
Barber, apprentice	330.371-014
Manicurist	331.674-010
Cosmetologist	332.271-010
Cosmetologist, apprentice	332.271-014
Hairstylist	332.271-018
Wig dresser	332.361-010
CHEFS, COOKS, AND MISCELLANEOUS FOOD PREPARATION:	
Cook	313.361-014
Cook, short order I	313.361-022
Cook, specialty foreign food	313.361-030
Cook, apprentice, pastry	313.381-018
Cook, school cafeteria	313.381-030
Cook, short order II	313.671-010
Cook, NOS**	313.999-999
Owner, restaurant	314.132-888
Cook, mess cook	315.361-010
Cook, psychiatric hospital	315.361-018
Pantry goods maker	317.684-014
Sandwich maker	317.684-018

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX B, TABLE 4 (continued)

CATEGORY OF "HIGH RISK" OCCUPATION	CODE NUMBER (DOT)
CHEFS, COOKS, AND MISCELLANEOUS FOOD PREPARATION, continued:	
Kitchen helper	317.687-010
Kitchen workers, n.e.c.#	318.687-010
APPAREL AND FURNISHINGS SERVICE:	
Presser, machine	363.682-018
Presser, hand	363.684-018
Presser, automatic	363.685-014
Presser, form	363.685-018
Shirt presser	363.685-026
Manager, laundromat	369.167-010
Manager, branch store	369.467-010
Laundry operator	369.684-014
PROCESSING:	
Plater	500.380-010
Baker helper	526.686-010
Box truck washer	529.687-018
Insecticide mixer	550.685-070
Press tender	556.685-066
Rubber tester	559.381-014
Washer, cleaner	599.687-030
MACHINE TRADES:	
Machinist	600.280-022
Gear machining	602.999-999
Grinder	603.280-010
Grinder	603.280-999
Lathe operator	604.685-026
Inspector, general, e.g. gager	609.684-010
Production machine tender	609.685-018
Loader-unloader, screen printing machine	652.686-022
Machinist, apprentice, wood	669.380-010
Barrel assembler	682.685-999
BENCHWORK:	
Engraver, hand, soft metals	704.381-030
Engraver, pantograph I	704.382-010
Engraver, pantograph II	704.682-014
Assembler, small parts	706.684-022
Bellows maker	714.684-010
Coil winder	724.684-026
Tube assembler	725.384-010
Electronics tester	726.281-014
Assembly, repair electrical equipment	729.999-999
Fishing rod assembler	732.684-066
Assembler, fire arms	736.381-010
Inspector, assembly, fire arms	736.387-010
Laborer, ammunition assembly	737.687-070

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APPENDIX B, TABLE 4 (continued)

CATEGORY OF "HIGH RISK" OCCUPATION	CODE NUMBER (DOT)
BENCHWORK, continued:	
Laborer, ammunition assembly	737.687-999
Painter, brush	740.684-999
Painter, spray	741.684-026
Rubber goods inspector tester	759.584-010
Fabrication, repair pottery & porcelain	774.684-999
Cutter, hand I	781-584-014
Cutter, hand II	781.687-026
STRUCTURAL WORK:	
Riveter	800.684-010
Riveter helper	800.687-010
Assembler, aircraft, structures & surfaces	806.381-026
Shipfitter	806.381-046
Shipfitter helper	806.687-050
Welder, arc	810.384-014
Welder, gas	811.684-014
Welder, fitter	819.361-010
Welder, NOS	819.999-030
Electrician	824.261-010
Electrician	825.381-030
Electronics mechanic	828.281-010
Precision assembler	828.381-014
Electrician helper	829.684-022
Painter helper, automotive	845.684-014
Roofer	866.381-010
MISCELLANEOUS:	
Laboratory assistant, metallurgical	011.281-010
Laboratory tester	029.261-010
Cleaner, hospital	323.687-010
Cleaner, housekeeping	323.687-014
Armed forces personnel	378.999-040
Cleaner, commercial, institutional	381.687-014
Cleaner, industrial	381.687-018
Industrial truck operator	921.683-050
Art work, brush, spray	970.381-022
Photoengraving printer	971.381-034
Stripper	971.381-050
Developer	976.681-010

* Dictionary of Occupational Titles (1977)
A code of "9" was entered in those sections of the DOT code in which information provided by the respondent was too vague or insufficient to assign a complete DOT code.

** NOS = Not otherwise specified
# n.e.c.= Not elsewhere classified

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

MAJOR REFERENCES USED TO CLASSIFY [illegible]
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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

THE UNIVERSITY OF TEXAS SCHOOL OF PUBLIC HEALTH

ERU STUDY ON ENVIRONMENT AND HEALTH

TIME STARTED: _____

SECTION A

A1. First, I would like to ask you some general background questions. What was the month and year of your birth?

_____ month _____ year

A2. In what city and state or foreign country were you born? 1 2

_____ city _____ state _____ foreign country

IF TEXAS, what county is that in? 3 5

_____

A3. In what state or foreign country was your mother born? 6 7

_____ state _____ foreign country

A4. In what state or foreign country was your father born? 8 9

_____ state _____ foreign country

A5. Most people in the United States have ancestors who come from other parts of the world. A list of countries is given on page 1 of this booklet (GIVE RESPONSE BOOKLET TO RESPONDENT). Which numbers represent the main countries of origin for your ancestors? (CODE UP TO FOUR ANSWERS)

[ ][ ] [ ][ ] [9 OK]

If 83 (other) please specify _____

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A5a. We will be using this booklet periodically during this interview. I'll tell you which page to turn to as the need arises. 10 17

8/19/80

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

A6. Do you consider yourself to be Hispanic, Mexican American, Black, Oriental, American Indian, Caucasian, or a member of another ethnic group?

1 HISPANIC	5 AMERICAN INDIAN
2 MEXICAN AMERICAN	6 CAUCASIAN
3 BLACK	7 OTHER
4 ORIENTAL	

A6a. To which ethnic group do you belong? _____

☐ 18

A7. Are you presently married, widowed, divorced, separated or never married. Common law relationships are to be considered married.

1 MARRIED/COMMON LAW	4 SEPARATED
2 WIDOWED	5 NEVER MARRIED
3 DIVORCED	9 DK

☐ 19

A8. *I'm going to be asking you several questions about the places you have lived and the jobs you have held in your life. It will be helpful to both of us if we put some dates that are important to you on this sheet.* HAND RESPONDENT MEMORY SHEET

In what year did you: finish your education _____
turn 16 _____
first get married _____
first child born _____
discharge from military _____
_____
_____

1914-1918	World War I	1947	Texas City disaster
1929	Depression (stock market crash)	1950-1953	Korean War
1941	Pearl Harbor	1961	Hurricane Carla
1939-1945	World War II	1963	John F. Kennedy assassinated
1945	President Roosevelt died	1974	President Nixon resigns

If there are other dates that are important to you, let's put them in.

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INTERVIEWER'S NOTES

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INTERVIEWER CHECK POINT

SECTION B

IF STUDY SUBJECT BORN IN OR BEFORE 1924, START RESIDENTIAL HISTORY IN 1940.
IF BORN AFTER 1924, YEAR OF BIRTH PLUS 16 = _____

B1. I am going to ask you a series of questions about all of the places you have lived for 6 months or longer since (1940, the beginning of World War II) (you were 16). What was the name of the city or town where you were living in 19___? (RECORD CITY IN COLUMN B2 AND GO TO B3.)

B2. What was the name of the city or town where you lived next? (nearest community)	B3. What state or foreign country was that in?	B4. What was the name of the county?	B5. IF IN STUDY AREA - What was the street address? PROSE FOR CROSS STREETS OR NAME, DISTANCE, AND DIRECTION OF NEAREST COMMUNITY.

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B6. Was that an urban or rural area?	B7. Did the drinking water come from the community supply, did you have your own well, buy bottled water, or something else. WRITE RESPONSES IN BOX - SPECIFY ELSE.	B8. Was this either a farm or a ranch? RECORD RESPONSE	B9. How long did you live there?	B10. IF IN STUDY AREA In what year did you move from this address? IF NOT IN STUDY AREA In what year did you move from this city or town? PROBE FOR AGE IF NECESSARY. GO TO B2 UNTIL CURRENT ADDRESS.
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	
1 U 2 R 9 DK		1 YES 2 NO 9 DK	yrs mos	

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B11. Did you ever live on a farm or ranch before you were 16?

[1 YES] [2 NO] [9 DK]

B11a. In total, how many years did you live on a farm or ranch before you were 16? ☐ 1

_____ years ☐☐ 2 3

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INTERVIEWER'S NOTES

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INTERVIEWER CHECK POINT

IF STUDY SUBJECT BORN IN OR BEFORE 1926, START OCCUPATIONAL HISTORY IN 1940.
IF BORN AFTER 1926, YEAR OF BIRTH PLUS 16 = _____

SECTION C

C1. Now I would like to ask you some questions about your work experience. I would like to know about all the jobs you have held for 6 months or longer, including different jobs with the same employer. This will take some careful thought so just take your time and we'll go *step by step.* *(RECORD EACH JOB INCLUDING PERIODS OF UNEMPLOYMENT).* Let's begin with the job you had [in 1940, the beginning of World War II] (when you were 16). RECORD BEGINNING YEAR IN C2 AND ASK C3.

C2. In what year did you begin your (very first) (next) job (with this employer)? USE AGE AS A PROBE.	C3. What was your job title?	C4. How long did you work on that job?	C5. Was this a part-time or a full time job? C5a. IF PART-TIME ASK - How many hours per week did you work?	C6. What did you do on that job?	C7. What kind of business or industry was this?	C8. In what city and state was this job? C8a. IF IN STUDY AREA What was the name of your employer? RECORD CITY AND STATE ON TOP LINE OF BOX; EMPLOYER ON BOTTOM LINE	C9. While with this employer, did your *type of work change?* IF "YES" GO TO C9	C10. While with this employer, did you have more than 1 job at the same time? GO TO C11 AND CONTINUE UNTIL *CURRENT OR LAST JOB*
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK
_____ YEAR		_____ YRS _____ MOS	1 FT 2 PT 3 DK _____ HOURS	NAIL			1 YES 2 NO 9 DK	1 YES 2 NO 9 DK

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

C11. Now I'm going to read a list of materials. Please use the list on page 3 of your booklet. I would like to know if you have ever been exposed regularly to these materials?

C12. Have you ever been exposed to:	C13. FOR EACH "YES": Did you wear a respirator when exposed to this material?	C14. FOR EACH "YES": ASK: ASK - Did this exposure occur during leisure activities such as hobbies, at home or at work?	C15. IF AT WORK - Was this while you were working at one of the jobs we discussed or a different place? IF DIFFERENT JOB, MARK AND GO TO C1-C10. CODE IF MATERIALS NOT WITH APPROPRIATE CODE.	IF DISCUSSED, GO TO C16. LOG CODE IN ALL CASES. C16a. Which job was this?	
01. Acrylonitrile	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	1
02. Arsenic	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	2
03. Asbestos	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	3
04. Benzene	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	4
05. Beryllium	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	5
06. Bischloromethyl ether	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	6
07. Ceramic fiber or dust	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	7
08. Chemical fertilizers	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	8
09. Chromium or chromates	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	9
10. Coke oven emissions, coke or coal tars	1 YES 2 NO 3 DK 4 REF	1 HOME 2 WORK 3 BOTH	DIFFERENT	DISCUSSED	10

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11. dyes, glues, lacquers or varnishes	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	31 33
12. fiberglass	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	34 36
13. cotton, grain, metal or wood dust	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	37 39
14. Insecticides, pesticides, herbicides and fungicides	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	40 42
15. isopropyl oil	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	43 45
16. paint sprays	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	46 48
17. petroleum products, pitch oil, asphalt	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	49 51
18. radioisotope or radio-active materials	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	52 54
19. vinyl chloride	9 DK 2 NO 1 YES	9 DK 2 NO 1 YES	3 HOBBY 4 HOME 5 WORK	DIFFERENT	DISCUSSED	55 57

C16. Over the years, what would you consider to be your usual occupation?

________________________ 58 66

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C17. Did any person or persons in your household other than yourself ever work in any of the following industries?	FOR EACH "YES" ASK C18.			How many years did you live with one or more persons working in this industry?	
1. manufacture of asbestos products	9 DK	2 NO	1 YES	_____	67 69
2. manufacture of cement	9 DK	2 NO	1 YES	_____	70 72
3. manufacture of insulation	9 DK	2 NO	1 YES	_____	73 75
4. coal mining	9 DK	2 NO	1 YES	_____	76 78
5. uranium mining	9 DK	2 NO	1 YES	_____	79 81
6. asbestos mining	9 DK	2 NO	1 YES	_____	82 84
7. shipbuilding/ shipyard work	9 DK	2 NO	1 YES	_____	85 87
8. demolition	9 DK	2 NO	1 YES	_____	88 90
9. high rise construction	9 DK	2 NO	1 YES	_____	91 93

C19. What is (was) the usual lifetime occupation of your father?

_____ 94 102

C20. What business or industry was this?

_____ 103 105

C21. What is (was) the usual lifetime occupation of your mother?

_____ 106 114

C22. What business or industry was this?

_____ 115 117

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INTERVIEWER CHECK POINT

IF NEVER MARRIED, GO TO C25.

C23. What is (was) the usual lifetime occupation of your husband wife?

_____

C24. What business or industry was this?

_____

118 [ ][ ][ ][ ][ ][ ][ ][ ] 125

127 [ ][ ][ ]

C25. Have you ever used aerosol hair spray at least once a week for a year or more?

1 YES 2 NO 9 DK

C25a. How many years was that? _____ yrs

130 [ ][ ][ ] 132

C26. Have you used a hand held hair dryer at least once a week for a year or more?

1 YES 2 NO 9 DK

C26a. How many years was that? _____ yrs

133 [ ][ ][ ] 135

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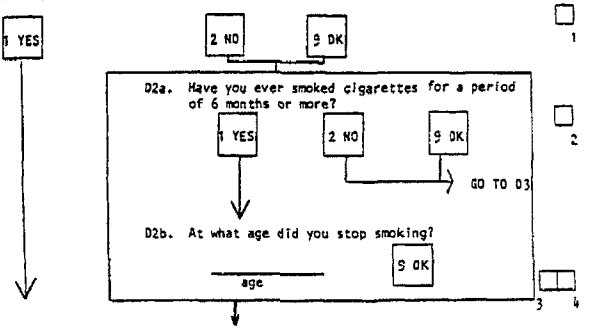
Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION D

D1. The next questions are about smoking. There are quite a few questions in this section because, for many people, smoking is a regular part of work and leisure activities and a way of relaxing or handling stress. Some of these questions may be hard for you to answer because you have to remember things you may not usually pay much attention to. Please try to be as accurate as possible because what you say is really important.

D2. First, do you smoke cigarettes?



D2c. At what age did you start smoking cigarettes?

age 5 6

D2d. Over the years, about how many cigarettes or packs of cigarettes have you smoked a day? 7 8

cigarettes packs

D2e. Over the years, would you consider yourself a light, moderate, or heavy smoker? 9

1 LIGHT | 2 MODERATE | 3 HEAVY | 9 DK

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

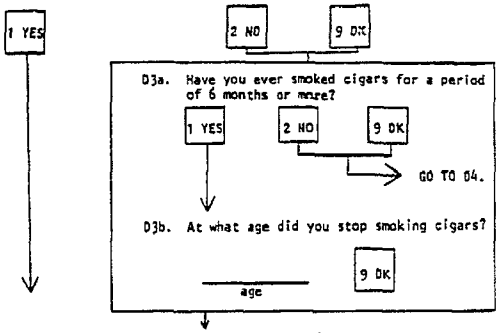
D2f. Do (did) you usually smoke filter or non-filter cigarettes?

10

D2g. Do (did) you usually smoke cigarettes you roll yourself?

11

D3. Do you smoke cigars?



12

13

14 15

D3c. At what age did you start smoking cigars?

_____ age

16 17

D3d. Over the years, about how many cigars have you smoked a day?

_____ # cigars

18 19

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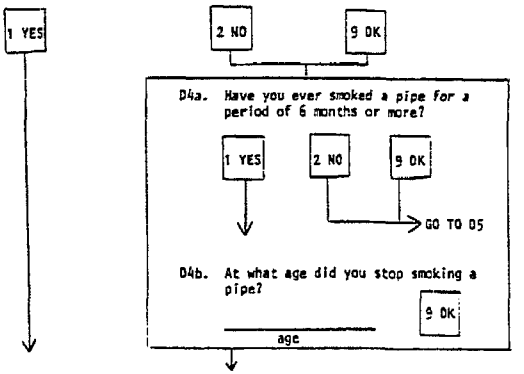
Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

04. Do you smoke a pipe?



20

21

22 23

D4c. At what age did you start smoking a pipe?

age

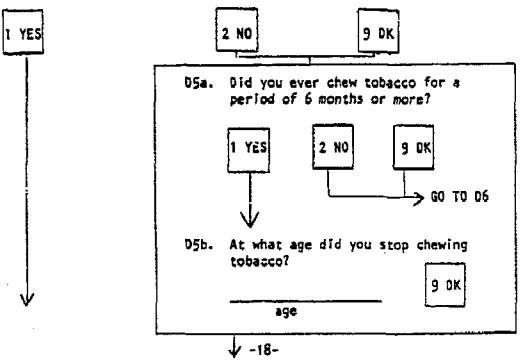
24 25

D4d. Over the years, about how many pipefuls of tobacco have you smoked a day?

pipes

26 27

05. Do you chew tobacco?



28

29

30 31

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

D5c. At what age did you start chewing tobacco?

_____ age

32 33

D5d. Over the years, about how much tobacco have you chewed per day?

_____

34 35

D6. Do you take snuff?

1 YES

2 NO

9 DK

36

D6a. Did you ever take snuff for a period of 6 months or more?

1 YES

2 NO

9 DK

GO TO D7

37

D6b. At what age did you stop taking snuff?

_____ age

9 DK

38 39

D6c. At what age did you begin taking snuff?

_____ age

40 41

D6d. Over the years, about how many pinches of snuff have you taken per day?

_____

42 43

D7. Did any member of your household smoke regularly while living with you, either when you were growing up or as an adult?

1 YES

2 NO

9 DK

GO TO E1

44

D7a. What was the total number of years that you lived with at least one person who smoked regularly?

_____ years

45 46

20636079797

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION E

E1. Many people drink alcoholic beverages such as beer, wine, or hard liquor (whiskey, gin, and so on) fairly regularly. Others drink them only on certain occasions. For some people drinking habits change during their lifetime, others drink about the same amount all their adult lives. We are interested in how often and how much you have drunk in certain periods of your life.

E2. Have you ever had at least 6 alcoholic beverages in a period of one year?

1 YES | 2 NO | 9 DK

GO TO F1

E3. To help you recall how often you drank alcoholic beverages, a list of the times when people frequently drink is on pages 4 and 5 of your booklet. (PAUSE)

E3a. Thinking back to when you were in your:	E3b. How often did you drink:			E3c. On the occasions when you drank beer (wine, hard liquor) how many drinks did you usually have?
20's	1 BEER	NOT AT ALL	yr mo wk day	qty.
	2 WINE	NOT AT ALL	yr mo wk day	qty.
	3 HARD LIQUOR	NOT AT ALL	yr mo wk day	qty.
	FOR STUDY SUBJECTS BORN AFTER 1945, GO TO F1.			
30's	1 BEER	NOT AT ALL	yr mo wk day	qty.
	2 WINE	NOT AT ALL	yr mo wk day	qty.
	3 HARD LIQUOR	NOT AT ALL	yr mo wk day	qty.
	FOR STUDY SUBJECTS BORN AFTER 1935, GO TO F1.			
40's	1 BEER	NOT AT ALL	yr mo wk day	qty.
	2 WINE	NOT AT ALL	yr mo wk day	qty.
	3 HARD LIQUOR	NOT AT ALL	yr mo wk day	qty.
	FOR STUDY SUBJECTS BORN AFTER 1925, GO TO F1.			

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

E3a. Thinking back to when you were in your:	E3b. How often did you drink:			E3c. On the occasions when you drank beer (wine, hard liquor) how many drinks did you usually have?
50's	1 BEER	NOT AT ALL	yr mo wk day	qty.
	2 WINE	NOT AT ALL	yr mo wk day	qty.
	3 HARD LIQUOR	NOT AT ALL	yr mo wk day	qty.
		↓	FOR STUDY SUBJECTS BORN AFTER 1915, GO TO F1.	
60's	1 BEER	NOT AT ALL	yr mo wk day	qty.
	2 WINE	NOT AT ALL	yr mo wk day	qty.
	3 HARD LIQUOR	NOT AT ALL	yr mo wk day	qty.
		↓ GO TO F1.		

2063630799

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION F

F1. Now we would like to get some information about your health. What has been your usual weight as an adult?

_____ POUNDS

1 3

F2. What is your height? _____ FEET _____ INCHES

4

F3. I am going to read you a list of conditions. Please tell me whether a doctor has ever told you that you had such a condition or illness.

1.	Cirrhosis	1 YES	2 NO	9 DK
2.	Chronic bronchitis	1 YES	2 NO	9 DK
3.	Bronchial asthma	1 YES	2 NO	9 DK
4.	Chronic obstructive pulmonary disease	1 YES	2 NO	9 DK
5.	Asbestosis	1 YES	2 NO	9 DK
6.	Silicosis	1 YES	2 NO	9 DK
7.	Anthracosilicosis, or black lung disease	1 YES	2 NO	9 DK
8.	Byssinosis or cotton mill fever	1 YES	2 NO	9 DK
9.	Cancer	1 YES	2 NO	9 DK

5 6 7 8 9 10 11 12 13

Please specify site(s)

_____

_____

14 16

2063630800

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

F4. Did a doctor ever tell you that you had tuberculosis or TB?

9 DK 2 NO 1 YES [ ] 17

F4a. What month and year was that?

_____ month _____ year [ ][ ][ ][ ] 18 21

F4b. What treatments did you receive?

_____

_____ [ ][ ] 22 23

F5. Altogether, how many brothers and sisters are there in your immediate family including any half brothers and sisters. Include any who are no longer living?

_____ TOTAL NUMBER OF BROTHERS AND SISTERS [ ][ ] 24 25

F6. Altogether, how many natural children have you ever had, including any who are no longer alive?

_____ TOTAL NUMBER OF NATURAL CHILDREN [ ][ ] 26 27

F7. We are interested in knowing about any types of cancer, including leukemia and Hodgkin's Disease, that may have occurred in your immediate family.

F7a. Did any of the following people ever have any type of cancer? IF YES GO TO F7b & F7c.				F7b. What type of cancer did he (she, they) have?	F7c. What was the age of your (relation) when the cancer was diagnosed?	
1. husband/wife	9 DK	2 NO	1 YES			[ ][ ] 28 31
2. father	9 DK	2 NO	1 YES			[ ][ ] 32 35
3. mother	9 DK	2 NO	1 YES			[ ][ ] 36 39
4. brothers	9 DK	2 NO	1 YES			[ ][ ] 40 43
5. sisters	9 DK	2 NO	1 YES			[ ][ ] 44 47
6. children	9 DK	2 NO	1 YES			[ ][ ] 48 51

2063630801

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION G

G1. Now I am going to ask you about how often you ate a number of different foods. I am interested in your typical or average diet about 4 years ago.

G1a. The first part of this section is a list of fruits and vegetables. Please tell me if you ate the following the entire year, primarily in certain seasons or not at all.			G1b. Now give me the number in total times per year or in a number of times per month or per week that you ate this food, whichever is more convenient. Pages 4 and 5 of your booklet contain list of possible answers. If you are not sure exactly how often the food was eaten, try to make a good guess.
01. A fresh tomato, or several cherry tomatoes	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
02. Any leafy green lettuce, such as Romaine or Boston lettuce	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
03. Carrots, fresh, frozen or canned, including servings in salads or stews	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
04. Green beans or string beans, fresh, frozen, or canned.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
05. Green peas, fresh, frozen, or canned.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

06. Green asparagus, fresh, frozen or canned.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
07. Avocado or guacamole	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
08. Corn, fresh, frozen, or canned.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
09. Summer squash, such as zucchini or yellow crookneck, fresh, frozen, or canned.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
10. Winter squash, such as butternut, Hubbard or acorn, including use in pie or soup	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
11. Sweet potatoes or yams or pumpkin including use in pie or soup	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day
12. Broccoli, fresh or frozen	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year	month	week	day

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

13. Greens, such as spinach, turnip greens, collard or mustard greens	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
14. Fresh cantaloupe	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
15. A slice of watermelon	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
16. Peaches, fresh, frozen, canned or dried	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
17. Fresh nectarines	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
18. Several apricots fresh, frozen, canned or dried	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
19. Half of a pink or red grapefruit	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

20. Sweet green peppers, fresh or frozen	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
21. Sweet red peppers, fresh, frozen, or pickled	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day
22. Hot red peppers or hot pepper sauce or chili powder used as a seasoning. Do not include jalapenos.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	5 SEASONALLY 6 ALL YEAR	year month week day

2063630805

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

GZ. Now I'm going to read another list of foods. Please give me the total number of times you ate each food using the choices on pages 4 and 5 of your booklet.

01. A serving of eggs, cooked any way, or in an omelet or quiche or souffle.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day
02. A glass of milk of any kind.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day
03. A serving of cheese, such as American, cheddar, mozzarella, brie, cream cheese - any hard or soft or processed cheese, including cheese eaten in a sandwich.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day
04. Cheese in a casserole or mixed dish, such as lasagna or pizza or cheese enchiladas.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day
05. A serving of ice cream, but do not include sherbet, ice milk, or frozen yogurt.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day
06. A pat of butter or margarine	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	____ year	____ month	____ week	____ day

2063630806

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

07. Chicken liver, whole or chopped.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
08. Beef liver or calves liver.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
09. Several prunes, dried or cooked, or a glass of prune juice.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
10. A glass of tomato or V8 juice, including any beverage containing tomato juice.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
11. A glass of grapefruit juice alone or mixed with orange and pineapple juice.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
12. Cooked tomatoes or tomatoes in a sauce such as spaghetti with tomato sauce, barbeque with a tomato-based sauce, or pizza.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day

2063630807

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

13. Corn tortillas, cornbread, corn grits or corn stuffing	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
14. A serving of super fortified cold cereal such as Total or Most.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day
15. A serving of any other cold cereal, such as corn flakes or Cheerios.	9 DK 2 NOT AT ALL 4 EATEN, DK WHEN	year month week day

2063630808

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

G3. Did you take any vitamin pills or supplements for more than a year since age 25?

1 YES | 2 NO | 9 DK

GO TO G4a.

	G3a. How long did you take this type supplement?	G3b. When was that?	G3c. How many times a day or week did you take this supplement on a regular basis?
1. Did you take multiple vitamin pills or tablets? (IF YES GO TO G3a.) 9 DK | 2 NO | 1 YES	____ years	19__ to 19__	____ per day ____ per week
2. *Did you take therapeutic* or high potency vitamin pills? (IF YES GO TO G3a.) 9 DK | 2 NO | 1 YES	____ years	19__ to 19__	____ per day ____ per week
3. Did you take Vitamin A capsules? (IF YES GO TO G3a.) 9 DK | 2 NO | 1 YES	____ years	19__ to 19__	____ per day ____ per week
4. Did you take cod liver oil? (IF YES GO TO G3a.) 9 DK | 2 NO | 1 YES	____ years	19__ to 19__	____ per day ____ per week

2063630809

G4. Did you take any other vitamin pills or supplements on a regular basis since age 25?

9 DK | 2 NO | 1 YES — Please specify _____

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

G4a. INTERVIEWER CHECK POINT

IF RESPONDENT WAS BORN AFTER 1925 GO TO PAGE 32, H1. →

IF RESPONDENT WAS BORN IN OR BEFORE 1925, ASK G5 AND G6. ↓

G5. When you compare your typical diet 4 or so years ago to your typical diet since age 45, do you consider it to be:

0 not changed very much	1 somewhat changed	2 significantly changed

G6. When you compare your typical diet 4 or so years ago to your typical diet between ages 25 and 45, do you consider it to be:

0 not changed very much	1 somewhat changed	2 significantly changed

2063630810

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION H

H1. I have a few last questions. What was the highest grade you completed in school?

00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17+

1 2

INTERVIEWER CHECK POINT: IF NEVER MARRIED GO TO H4.

H2. MARRIED STUDY SUBJECTS ONLY. What was the highest grade your husband/wife completed in school?

00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17+

3 4

H3. FOR MARRIED FEMALE STUDY SUBJECTS ONLY. What is your maiden name?

_____

H4. Do you have a current Texas driver's license?

1 YES 2 NO 9 DK

5

H4a. Is the address on your driver's license correct?

1 YES 2 NO 9 DK

6

H5. What was your religious preference as you were growing up (before you were 16)?

1 PROTESTANT → H5a. What denomination was that? _____

2 CATHOLIC → GO TO H6

3 JEWISH → GO TO H6

7 OTHER → H5b. What was that? _____

9 DK → GO TO H6.

7 8

H6. Thank you very much for answering these questions. Your participation in this research will be very helpful.

My office at The University of Texas School of Public Health may wish to get in touch with you by phone or mail to confirm this interview.

TIME ENDED _____

2063630811

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

SECTION I

INTERVIEWER ASSESSMENT

(Complete as soon as possible after

completion of interview)

SECTION BY SECTION

I1. Section B - The quality of responses in the residential history section is:

- [1] High quality
- [2] Generally reliable
- [3] Questionable
- [4] Unsatisfactory

☐ 1

I2. Section C - The quality of responses in the occupational history section is:

- [1] High quality
- [2] Generally reliable
- [3] Questionable
- [4] Unsatisfactory

☐ 2

I3. Section D - The quality of responses in the smoking history section is:

- [1] High quality
- [2] Generally reliable
- [3] Questionable
- [4] Unsatisfactory

☐ 3

2063630812

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

14. Section E - The quality of responses in the alcohol history section is:

[1] High quality
[2] Generally reliable
[3] Questionable
[4] Unsatisfactory

☐ 5

15. Section G - The quality of responses in the nutrition section is:

[1] High quality
[2] Generally reliable
[3] Questionable
[4] Unsatisfactory

☐ 6

OVERALL ASSESSMENT

16. Respondent's cooperation was:

[1] Very good
[2] Good
[3] Fair
[4] Poor

☐ 7

17. The quality of the responses in this interview are:

[1] High quality
[2] Generally reliable
[3] Questionable
[4] Unsatisfactory

☐ 8

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

FOR OVERALL QUESTIONABLE OR UNSATISFACTORY RESPONSES ONLY.

18. The main reason for the unsatisfactory or questionable quality is that the respondent:

[1] was ill or disabled
[2] spoke English poorly
[3] was evasive or suspicious
[4] was bored or uninterested
[5] was upset or depressed by topic
[6] was drunk or mentally disturbed
[7] had poor hearing, speech or vision
[8] was confused by frequent interruptions
[9] was insufficiently knowledgeable
[10] other (specify) _____

_____

9 10

20630814

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

THE UNIVERSITY OF TEXAS SCHOOL OF PUBLIC HEALTH

Epidemiology Research Unit Respiratory Cancer Studies

HOSPITAL ABSTRACT — 1

Study Number [1–9]

Abstractor _____ Date of Abstract (mo., day, yr.) [10–15]

Hospital _____ (name and location) [16–18]

Hospital Chart Number [19–28]

Date Admitted (mo., day, yr.) [29–34]

Date Discharged/Died (mo., day, yr.) [35–40]

Name _____ (last, first, middle, maiden)

Address _____ (street) City [41–43]

Zip Code [44–48]

County: 039 Brazoria 167 Galveston 245 Jefferson
071 Chambers 201 Harris 361 Orange [49–51]

Telephone Number _____ Spouse _____ (last name, first)

Contact: 1 - Next of kin 2 - Neighbor/Friend 3 - Employer 4 - Other 9 - Unknown [52]

_____ name (last, first) _____ relationship

_____ address _____ phone

Social Security Number [53–61]

Date of Birth (mo., day, yr.) [62–67]

Race: 0 - Caucasian
1 - Caucasian of Spanish Surname, of Spanish Origin
2 - Black
3 - American Indian
4 - Chinese
5 - Japanese
6 - Filipino
7 - Hawaiian
8 - Other
9 - Unknown [68]

Sex: 0 - Male 1 - Female [69]

Marital Status: 0 - Single (Never Married) 1 - Married 2 - Separated 3 - Divorced 4 - Widowed 9 - Unknown [70]

Type of Patient: 0 - Inpatient 1 - Outpatient [71]

Was first diagnosis of this neoplasm made elsewhere?
0 - Yes 1 - No 9 - Unknown [72]

If diagnosis is made elsewhere:
Hospital and/or Physician and Location:

_____

_____

Diagnosis (Primary Site and Cell Type):

_____

Date of first diagnosis: [73–78]

DISTRIBUTION
WHITE/YELLOW — ERU Copies
PINK — SCRP Copy
GOLDENROD — Hospital Copy

2063630815

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Final Diagnosis at this institution: _____

_____

_____

I.C.D. Code (Anatomical Site) [ ] 78 82

Histological Type of Tumor [ ] 83 87

Grade of Tumor: 0 - Grade I, well differentiated
1 - Grade II, moderately differentiated
2 - Grade III, poorly differentiated
3 - *Grade IV, undifferentiated*
9 - Unspecified [ ] 88

Extent of Disease: (Pathology report and diagnostic evidence used for staging)

Basis of Diagnosis: 0 - Autopsy
1 - Histology (surg/biopsy tissue)
2 - Cytology
3 - Hematology
4 - Diagnostic Radiology
5 - Immunology
6 - *Biochemical*
7 - Clinical only
8 - Other (specify)
9 - Unknown [ ] 89

Stage of Disease: 0 - In situ
1 - Localized
2 - Regionalized with direct extension to adjacent tissues
3 - *Regional with regional node* involvement
4 - Regional with regional nodes plus direct extension
5 - Regional, not otherwise specified
6 - Distant or diffuse spread
7 - Not enough information *to stage*
9 - Not recorded [ ] 90

Date of Death: (mo., day, yr.) [ ] 91 96

Primary Cause of Death - I.C.D. Code [ ] 97 100

_____

Secondary Cause of Death - I.C.D. Code [ ] 101 104

_____

Autopsy Performed: 0 - Yes 1 - No 9 - Unknown [ ] 105

Referring Physician (Physician responsible for follow-up) [ ] 106 110

_____

Attending Physician _____ [ ] 111 115

REMARKS: (Occupation, smoking/alcohol/history of lung disease, etc.)

2063630816

FOLLOW-UP OF LIVING CASES

Vital Status: 0 - Living 1 - Dead 9 - Unknown [ ] 116

Date of Contact (mo., day, yr.) [ ] 117 122

REMARKS:

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Texas Department of Health
CONFIDENTIAL CANCER REGISTRY ABSTRACT FORM

Patient

1-6 REGISTRY NUMBER
7-9 HOSPITAL
10-19 C [illegible] HOSPITAL CHART NUMBER
DATE ADMISSION / DATE DISCHARGE
20-45 NAME:
RESIDENCE:
50-87
88-92 ZIP CODE / TELEPHONE NUMBER
93-95 101 COUNTY Harris
96-106 SOCIAL SECURITY NUMBER
107-109 PLACE OF BIRTH NA
110-114 999 COUNTY OF BIRTH NA
115-120 DATE OF BIRTH

2 2 RACE & ETHNICITY
3 1 SEX
4 3 MARITAL STATUS
5 [illegible] RELIGION Baptist
PRIMARY CONTACT WITH ARE ATTRESS: (RELATIONSHIP)

History

12 C CLASS OF CASE
13 C TYPE OF PATIENT
14 1 WAS FIRST DIAGNOSIS MADE ELSEWHERE
15-18 DATE OF FIRST DIAGNOSIS
FIRST DIAGNOSIS MADE AT/BY:
DIAGNOSIS:
SITES OF OTHER NEOPLASMS:
21 STAGE OF DISEASE AT FIRST DIAGNOSIS
22-27 DATE OF INITIAL TREATMENT
28 TYPE OF TREATMENT
29
30
31
32 C SEQUENCE OF THIS TUMOR

Remarks

OCCUPATION:
SMOKING HISTORY: Two ppd for ~~40~~ 45 yrs.
ALCOHOL HISTORY: Occasionally drinks alcohol
FAMILY HISTORY OF CANCER: mother died of abdominal CA
CHIEF COMPLAINT: Episodes of lightheadedness Increased difficulty in swallowing over last 4 wks has noticed increasing dyspnea, SOB.

Diagnosis

45-54 12-16-77 DATE OF DIAGNOSIS
55-59 8070/3 I.C.D.-O MORPHOLOGY CODE
60 3 GRADE OF TUMOR Anaplastic CA
61-64 16.3 FINAL DIAGNOSIS:
(I.C.D. CODE) Anaplastic small cell undifferentiated CA
12-16-77 27-1853 Tissue from right upper lung biopsy reveals small cell bronchial ca consistent w/ oat cell ca.
65-66 SIZE OF PRIMARY TUMOR NP
67 1 BASIS OF DIAGNOSIS
68 4 STAGE OF DISEASE
EXTENT OF DISEASE
12-15-77 27-21304 Supraclavicular area: subtotal collapse of superior vena cava by tumoral compression primarily and metastatic 12-20-77 27-1937 Liver within normal limits

Treatment

69 0 WAS TREATMENT COMPLETED?
70 C INTENT OF THERAPY
71-74 1277 DATE FIRST COURSE DEFINITIVE TREATMENT STARTED
75-78 DATE FIRST COURSE DEFINITIVE TREATMENT COMPLETED
81 1 TYPE OF TREATMENT TO THIS TUMOR
12-16-77 Bronchoscopy
82 12-17-77 Radiotherapy - 3 doses
83 To be seen at M.D. Anderson
84

Condition

85 2 CONDITION AT DISCHARGE
86-91 071978 DATE OF DEATH Bush 5353c
92-95 1629 PRIMARY CAUSE OF DEATH
96-99 SECONDARY CAUSE OF DEATH
100 1 AUTOPSY PERFORMED

Follow-up

100-105 PHYSICIAN
106-110 PHYSICIAN
111-115 PHYSICIAN
116-120 PHYSICIAN
121 0 TRANSACTION CODE
122 1 TAPE NUMBER 1/22/80
DATE ABSTRACTED / ABSTRACTOR

2063630817

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C

Detailed Tables of Results

2063630818

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 1

USUAL OCCUPATION OF MOTHERS AND FATHERS OF LUNG CANCER CASES AND COMPEERS.

CATEGORIES OF OCCUPATIONS	MOTHER				FATHER			
	Cases		Compeers		Cases		Compeers	
	No.	%	No.	%	No.	%	No.	%
Professional, Technical, and Managerial (001-199)	12	4.8	7	2.6	45	18.7	41	15.0
Clerical and Sales (201-299)	17	6.8	12	4.7	30	12.4	21	8.2
Service (301-389)*	207	82.5	237	86.5	9	3.3	12	4.7
Agricultural, Fishery, Forestry, and related (401-461)	6	2.4	7	2.6	71	29.5	95	37.1
Processing (500-599)	2	.8	2	.7	5	2.1	7	2.7
Machine Trades (600-699)	0		2	.7	19	7.9	26	10.1
Benchwork (700-799)	6	2.4	6	2.2	5	2.1	3	1.2
Structural Work (800-899)	1	.4			32	13.3	33	12.8
Miscellaneous (900-979)					26	10.8	29	11.3
Total	251	100.0	274	100.0	241	100.0	257	100.0
Unknown:	9		4		15		14	
Unemployed, retired, on welfare, disabled:					3		7	
Total	259		278		259		278	

*Service occupations of Mothers include housewife :
Cases' Mothers = 200 (96.6% of Service)
Compeers' Mothers = 224 (94.5% of Service)

2063630819

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 1

USUAL INDUSTRY OF MOTHERS AND FATHERS OF LUNG CANCER CASES AND COMPEERS.

CATEGORIES OF INDUSTRIES	MOTHER				FATHER			
	Cases		Compeers		Cases		Compeers	
	No.	%	No.	%	No.	%	No.	%
Agriculture, Forestry, and Fishing (0100-0971)	6	12.0	7	14.3	71	29.6	84	32.6
Mining (1000-1499)					19	7.9	13	5.0
Construction (1500-1799)	1	2.0			25	10.4	27	10.5
Manufacturing (2000-3999)	6	12.0	9	18.4	42	17.5	41	15.9
Transportation, Communications, Electric, Gas and Sanitary Services (4000-4971)	2	4.0	4	8.2	23	9.6	27	10.5
Wholesale Trade (5000-5199)	1	2.0			11	4.6	4	1.6
Retail Trade (5200-5999)	10	20.0	10	20.4	12	5.0	24	9.2
Finance, Insurance, and Real Estate (6000-6799)	3	6.0	4	8.2	8	3.3	4	1.6
Services (7000-8999)	19	38.0	15	30.6	22	9.2	27	10.5
Public Administration (9100-9721	2	4.0			6	2.5	7	2.7
Total	50	100.0	49	100.0	240	100.0	258	100.0
Unemployed, retired, on welfare, disabled, not applicable:	203		226		4		4	
Unknown:	6		3		15		16	
Total	259		278		259		278	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 3

AGE DISTRIBUTION OF FEMALE
LUNG CANCER CASES AND COMPEERS.

Age groups#	Cases No.	Cases %	Compeers No.	Compeers %
30 - 39 years	2	.8	4	1.4
40 - 44 years	6	2.3	3	1.1
45 - 49 years	17	6.6	25	9.0
50 - 54 years	40	15.4	39	14.0
55 - 59 years	52	20.1	52	18.7
60 - 64 years	60	23.2	50	18.0
65 - 69 years	38	14.7	57	20.5
70 - 74 years	32	12.4	27	9.7
75 or more years	12	4.6	21	7.6
Total	259	100.0	278	100.0

Age estimated by subtracting date of birth from 1 January, 1979. Study eligibilty = 35 yr to 79 yr age.

Chi-square estimated using 8 age groups (no cell with n < 5) = 8.53, 7 d.f., not significant at 5%.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 4

VITAL STATUS OF FEMALE LUNG CANCER CASES AND COMPEERS.

Vital status	Cases No.	Cases %	Compeers No.	Compeers %
Living	44	17.0	78	28.1
Deceased	215	83.0	200	71.9
Total	259	100.0	278	100.0

Chi-square: 10.00, p. = < 0.05.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 5a

STATE OF BIRTH OF FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS.

	Living					Deceased			
State of birth	Cases No.	%	Compeers No.	%	State of birth	Cases No.	%	Compeers No.	%
Texas	14	31.8	39	50.0	Texas	128	59.5	108	54.0
Other	30	68.2	39	50.0	Other	87	40.5	92	46.0
Total	44	100.0	78	100.0	Total	215	100.0	200	100.0

Chi Square: 4.56, α = <0.05 Chi Square: 1.08, n.s.‡

APPENDIX C TABLE 5b

COUNTY OF BIRTH OF FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS.

	Living					Deceased			
County of birth	Cases No.	%	Compeers No.	%	County of birth	Cases No.	%	Compeers No.	%
Harris	4	9.1	8	10.3	Harris	21	9.8	21	10.5
Other	40	90.9	70	89.7	Other	194	90.2	179	89.5
Total	44	100.0	78	100.0	Total	215	100.0	200	100.0

Chi Square: 0.27, n.s. Chi Square: 0.17, n.s.
‡ n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 6

HIGHEST GRADE IN SCHOOL ATTAINED BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS

School grade attained	Cases No.	Cases %	Compeers No.	Compeers %
Living				
0 - 12	29	65.9	49	63.6
13 - 17	15	34.1	28	36.4
Total	44	100.0	77	100.0
Deceased				
0 - 12	141	67.8	146	76.4
13 - 17	67	32.2	45	23.6
Total	208	100.0	191	100.0

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 7

MARITAL STATUS OF FEMALE LUNG CANCER CASES
AND COMPEERS BY VITAL STATUS

	Living				Deceased			
	Cases		Compeers		Cases		Compeers	
Marital status	No.	%	No.	%	No.	%	No.	%
Married	23	52.3	56	71.8	114	53.0	119	59.5
Widowed	9	20.5	17	21.8	62	29.0	52	26.0
Divorced	10	22.7	4	5.1	33	15.4	25	12.5
Separated	1	2.3			3	1.4	1	.5
Never married	1	2.3	1	1.3	3	1.4	3	1.5
Total	44	100.0	78	100.0	215	100.5	200	100.0

Chi-square‡: 10.74 2.85
p value (2 d.f.) = < 0.05 > 0.05

‡Chi-square estimated using 3 categories: married, widowed, divorced or separated.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 3

AGE DISTRIBUTION OF FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS

	Living				Deceased			
	Cases		Compeers		Cases		Compeer	
Age groups*	No.	%	No.	%	No.	%	No	%
30 - 34 years			1	1.3			1	.5
35 - 39 years			1	1.3	2	.9	1	.5
40 - 44 years	1	2.3	2	2.6	5	2.3	1	.5
45 - 49 years	1	2.3	2	2.6	16	7.4	22	11.5
50 - 54 years	10	22.7	22	28.2	30	14.0	17	8.5
55 - 59 years	13	29.5	21	26.9	39	18.1	31	15.5
60 - 64 years	10	22.7	13	16.7	50	23.3	37	18.5
65 - 69 years	3	6.8	11	14.1	35	16.3	46	23.0
70 - 74 years	4	9.1	2	2.6	28	13.0	25	12.5
75 + years	2	4.5	3	3.8	10	4.7	18	9.0
Total	44	100.0	78	100.0	215	100.0	200	100.0

Chi-square = 1.26 (n.s) Chi-square = 2.86 (n.s.)

* Age estimated by subtracting date of birth from 1 January, 1979.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 9a

ODDS RATIOS FOR AGE FEMALE LUNG CANCER CASES AND COMPEERS STARTED TO SMOKE CIGARETTES, ALL SMOKERS

Age started	CASES No.	%	COMPEERS No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never	12	4.7	112	41.2	1.00				
30+ yr	23	9.1	23	8.5	9.33	4.07	21.40	33.37	< 0.05
21 - 29 yr	47	18.6	34	12.5	12.90	6.15	27.07	55.87	< 0.05
19 - 20 yr	40	15.8	29	10.7	12.87	6.00	27.62	52.53	< 0.05
17 - 18 yr	53	20.9	33	12.1	14.99	7.17	31.33	64.13	< 0.05
6 - 16 yr	78	30.8	41	15.1	17.76	8.77	35.94	81.28	< 0.05
Total	253	100.0	272	100.0	13.75‡	10.15	18.64	285.77	< 0.05
Unknown:	6		6						

‡ Mantel-Haenszel estimate.

APPENDIX C TABLE 9b

AGE FEMALE LUNG CANCER CASES AND COMPEERS STARTED TO SMOKE CIGARETTES, ALL SMOKERS.

Age started	CASES No.	%	COMPEERS No.	%
30+ yr	23	9.5	23	14.4
21 - 29 yr	47	19.5	34	21.3
19 - 20 yr	40	16.6	29	18.1
17 - 18 yr	53	22.0	33	20.6
6 - 16 yr	78	32.4	41	25.6
Total	241	100.0	160	100.0
Unknown:	6		6	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 10a

AGE FEMALE LUNG CANCER CASES AND COMPEERS STOPPED SMOKING CIGARETTES, ALL SMOKERS

Age stopped	Cases No.	Cases %	Compeers No.	Compeers %
19-37yr	2	3.3	17	32.1
38-50yr	8	13.1	16	28.6
51-57yr	21	34.4	15	26.8
58+ yr	30	49.2	12	21.4
Total	61	100.0	56	100.0

APPENDIX C TABLE 10b

ODDS RATIOS FOR AGE FEMALE LUNG CANCER CASES AND COMPEERS STOPPED SMOKING CIGARETTES

Age stopped	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	16.4	112	66.7	1.00				
19-37yr	2	2.7	17	7.7	1.44	.29	7.14	.20	n.s.
38-50yr	8	11.0	16	9.5	4.67	1.63	13.16	9.67	0.05
51-57yr	21	28.8	15	8.9	12.07	5.36	31.84	40.35	0.05
58+ yr	30	41.1	12	7.1	23.33	9.53	57.16	83.70	0.05
Total	73	100.0	168	100.0	9.67‡	6.23	14.91	102.11	0.05

‡ Mantel-Haenszel estimate.
Age stopped smoking unknown for 1 Case.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 11

ODDS RATIOS FOR TYPE OF CIGARETTE USUALLY SMOKED BY FEMALE LUNG CANCER CASES AND COMPEERS

Type of cigarette	Cas No.	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	12	112	47.3	1.00				
Non-filter	47	38	16.0	11.54	5.55	24.03	51.30	< 0.05
Filter	129	78	32.9	15.44	7.99	29.82	87.98	< 0.05
Self-rolled	32	9	3.8	33.19	12.84	85.75	72.65	< 0.05
Total	220	237	100.0					
Mantel-Haenszel estimate:				15.99	10.93	23.39	203.98	< 0.05
Unknown:	1	2						

NOTE:
Cases and compeers used different types of cigarettes throughout their lifetime and, consequently, there is overlap among the types of cigarettes reported as smoked. In addition, a "no" response to the question asking if they usually smoked self-rolled cigarettes is omitted because of possible ambiguity in the question. Case responses of "no" = 64 and Compeers = 45.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 12

USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY LUNG FEMALE CANCER CASES AND COMPEERS, ALL SMOKERS.

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %
Less than 20	21	8.8	42	25.6
20	76	31.9	60	36.6
More than 20	141	59.2	62	37.8
Total	238	100.0	164	100.0
Unknown:	9		2	
Mean:	31.5		24.6	
Standard deviation:	14.81		13.24	

USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY LUNG FEMALE CANCER CASES AND COMPEERS. CURRENT SMOKERS.

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %
Less than 20	12	6.7	20	18.2
20	52	28.9	41	37.3
More than 20	116	64.4	49	44.5
Total	180	100.0	110	100.0
Mean:	32.4		26.9	
Standard deviation:	14.52		12.89	

USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY LUNG FEMALE CANCER CASES AND COMPEERS, EXSMOKERS.

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %
Less than 20	9	15.5	22	40.7
20	24	41.4	19	35.2
More than 20	25	43.1	13	24.1
Total	58	100.0	54	100.0
Mean:	28.6		19.7	
Standard deviation:	15.45		17.41	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 13

ODDS RATIOS FOR USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY FEMALE LUNG CANCER CASES AND COMPEERS, ALL SMOKERS

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	4.8	112	40.6	1.00				
Less than 20	21	8.4	42	15.2	4.67	2.11	10.31	16.09	< 0.05
20	76	30.4	60	21.7	11.82	5.96	23.45	61.84	< 0.05
More than 20	141	56.4	62	22.5	21.23	10.90	41.32	110.50	< 0.05
Total	250	100.0	276	100.0	12.09‡	8.44	17.32	184.77	< 0.05
Unknown:	9		2						
Mean among smokers:	31.5		24.6						
S.D.+	14.81		13.24						

CURRENT SMOKERS

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	6.3	112	50.5	1.00				
Less than 20	12	6.3	20	9.0	5.60	2.21	14.21	15.13	< 0.05
20	52	27.1	41	18.5	11.84	5.75	24.38	54.63	< 0.05
More than 20	116	60.4	49	22.1	22.10	11.16	43.73	105.46	< 0.05
Total	192	100.0	222	100.0	13.77‡	9.32	20.33	173.96	< 0.05
Mean among smokers:	32.4		26.9						
S.D.	14.52		12.69						

EXSMOKERS

Cigarettes smoked/day	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	17.1	112	67.5	1.00				
Less than 20	9	12.9	22	13.3	3.82	1.44	10.15	7.93	< 0.05
20	24	34.3	19	11.4	11.79	5.06	27.49	40.19	< 0.05
More than 20	25	35.7	13	7.8	17.95	7.32	43.99	51.97	< 0.05
Total	70	100.0	166	100.0	9.89‡	6.24	15.68	95.12	< 0.05
Mean among smokers:	28.6		19.7						
S.D.	15.45		13.41						

‡ Mantel-Haenszel estimate.
+ Standard deviation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 14

NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES. ALL SMOKERS:

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %
1 - 30 yr	52	21.8	57	35.4
31 - 40 yr	97	40.6	62	38.5
41 + yr	90	37.7	42	26.1
Total	239	100.0	161	100.0
Unknown:	8		5	
Mean:	37.3		32.3	
S.D.+	9.06		13.53	

CURRENT SMOKERS:

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %
1 - 30 yr	36	20.0	24	22.4
31 - 40 yr	74	41.1	47	43.9
41 + yr	70	38.9	36	33.6
Total	180	100.0	107	100.0
Mean:	37.9		36.4	
S.D.	8.85		11.06	

EXSMOKERS:

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %
1 - 30 yr	16	3.9	33	30.8
31 - 40 yr	23	12.8	15	14.0
41 + yr	20	11.1	6	5.6
Total	59	32.8	54	50.5
Mean:	36.2		24.0	
S.D.	10.8		14.29	

+ S.D. = Standard deviation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 15

ODDS RATIOS FOR NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES, ALL SMOKERS

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	4.8	112	41.0	1.00				
1 - 30 yr	52	20.7	57	20.9	8.51	4.21	17.22	42.11	< 0.05
31 - 40 yr	97	38.6	62	22.7	14.60	7.43	28.69	77.51	< 0.05
41 + yr	90	35.9	42	15.4	20.00	9.94	40.23	91.30	< 0.05
Total	251	100.0	273	100.0	13.64‡	9.57	19.45	208.23	< 0.05
Unknown:	8		5						
Mean among smokers:	37.3		32.2						
S.D.+	9.06		13.53						

CURRENT SMOKERS

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	6.3	112	51.1	1.00				
1 - 30 yr	36	18.8	24	11.0	14.00	6.37	30.79	53.11	< 0.05
31 - 40 yr	74	38.5	47	21.5	14.70	7.31	29.55	71.24	< 0.05
41 + yr	70	36.5	36	16.4	18.15	8.85	37.22	79.13	< 0.05
Total	192	100.0	219	100.0	15.63‡	10.79	22.65	201.91	< 0.05
Mean among smokers:	37.9		36.4						
S.D.	8.85		11.06						

EXSMOKERS

Years smoked	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	16.9	112	67.5	1.00				
1 - 30 yr	16	22.5	33	19.9	4.53	1.95	10.52	13.67	< 0.05
31 - 40 yr	23	32.4	15	9.0	14.31	5.93	34.56	44.40	< 0.05
41 + yr	20	28.2	6	3.6	31.11	10.47	92.48	57.91	< 0.05
Total	71	100.0	166	100.0	10.62‡	6.74	16.72	104.05	< 0.05
Mean among smokers:	36.2		24.0						
S.D.	10.80		14.29						

‡ Mantel-Haenszel estimate.
+ S.D. = Standard deviation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 16
PACK-YEARS OF CIGARETTES* SMOKED BY
FEMALE LUNG CANCER CASES AND COMPEERS

Pack-years of cigarettes	Cases No.	Cases %	Compeers No.	Compeers %
1 - 16.42	9	3.4	32	20.3
16.43 - 34.21	44	18.9	31	19.6
34.22 - 43.80	28	12.0	31	19.6
43.81 - 65.70	62	26.6	33	20.9
65.71+	91	39.1	31	19.6
Total	233	100.0	158	100.0
Unknown:	14		8	

* Pack-years = number of packs (20 cigarettes) X number of years smoked.

APPENDIX C TABLE 17

ODDS RATIOS FOR PACK-YEARS OF CIGARETTES* SMOKED
BY FEMALE LUNG CANCER CASES AND COMPEERS

Pack-years of cigarettes	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	12	4.9	112	41.5	1.00				
1 - 16.42	9	3.3	32	11.9	2.33	.98	6.20	3.91	n.s.
16.43 - 34.21	44	18.0	31	11.5	13.25	6.24	28.10	55.46	< 0.05
34.22 - 43.80	28	11.4	31	11.5	9.43	3.85	19.47	33.41	< 0.05
43.81 - 65.70	62	25.3	33	12.2	17.84	8.45	36.38	74.29	< 0.05
65.71+	91	37.1	31	11.5	27.40	13.32	56.37	106.46	< 0.05
Total	245	100.0	270	100.0	12.60**	9.28	17.11	263.71	< 0.05
Unknown:	14		8						

* Pack-years = number of packs (20 cigarettes/pack) X number years smoked.
** Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 19

AGE DISTRIBUTION OF FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS, ALL SMOKERS

Age group (5 years)	Cases No.	Cases %	Compeers No.	Compeers %
30 - 49 yr	24	9.7	21	12.7
50 - 64 yr	148	59.9	92	55.4
65 + yr.	75	30.4	53	31.9
Total	247	100.0	166	100.0

CURRENT SMOKERS:

Age group (5 years)	Cases No.	Cases %	Compeers No.	Compeers %
30 - 49 yr.	21	11.4	15	13.6
50 - 64 yr.	117	63.2	66	60.0
65 + yr.	47	25.4	29	26.4
Total	185	100.0	110	100.0

EXSMOKERS:

Age group (5 years)	Cases No.	Cases %	Compeers No.	Compeers %
30 - 49 yr.	3	4.8	6	10.7
50 - 64 yr.	31	50.0	26	46.4
65 + yr.	28	45.2	24	42.9
Total	62	100.0	56	100.0

NEVER SMOKED:

Age group (5 years)	Cases No.	Cases %	Compeers No.	Compeers %
30 - 49 yr.	1	8.3	11	9.8
50 - 64 yr.	4	33.3	49	43.8
65 + yr.	7	58.3	52	46.4
Total	12	100.0	112	100.0

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 19

SMOKING STATUS AND VITAL STATUS OF LUNG CANCER CASES AND COMPEERS.

	CASES						COMPEERS					
	All		Living		Deceased		All		Living		Deceased	
Smoking status	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All smokers	247	95.4	42	95.5	205	95.3	166	59.7	42	53.8	124	62.0
Exsmokers	62	23.9	19	43.2	43	20.0	56	20.1	22	28.2	34	17.0
Current smokers	185	71.4	23	52.3	162	75.3	110	39.6	20	25.6	90	45.0
Nonsmokers	12	4.6	2	4.5	10	4.7	112	40.3	36	46.2	76	38.0
Total	259	100.0	44	100.0	215	100.0	278	100.0	78	100.0	200	100.0

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 20

AGE LUNG CANCER CASES AND COMPEERS STARTED TO SMOKE CIGARETTES, ALL SMOKERS BY VITAL STATUS

Age started	CASES No.	CASES %	COMPEERS No.	COMPEERS %
Living:				
30+ yr	1	2.4	4	9.5
21 - 29 yr	10	23.8	11	26.2
19 - 20 yr	6	14.3	7	16.7
17 - 18 yr	14	33.3	13	31.0
6 - 16 yr	11	26.2	7	16.7
Total	42	100.0	42	100.0
Deceased:				
30+ yr	22	11.1	19	16.1
21 - 29 yr	37	18.6	23	19.5
19 - 20 yr	34	17.1	22	18.6
17 - 18 yr	39	19.6	20	16.9
6 - 16 yr	67	33.7	34	28.8
Total	199	100.0	118	100.0

2060630837

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 21

AGE FEMALE LUNG CANCER CASES AND COMPEERS STOPPED SMOKING CIGARETTE ALL SMOKERS BY VITAL STATUS

Age Stopped	Cases No.	Cases %	Compeers #	Compeers %
Living:				
19-37yr	0		6	27.3
38-50yr	1	5.3	9	36.4
51-57yr	10	52.6	6	27.3
58+ yr	8	42.1	1	9.1
Total	19	100.0	22	100.0
Deceased:				
19-37yr	2	4.8	7	20.6
38-50yr	7	16.7	8	23.5
51-57yr	11	26.2	9	26.5
58+ yr	22	52.4	10	29.4
Total	42	100.0	34	100.0

2063630838

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 22

USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS

Number of cigarettes per day	Living Cases No.	%	Compeers No.	%
Less than 20	4	9.8	15	36.6
20	15	36.6	17	41.5
More than 20	22	53.7	10	24.4
Total	41	100.0	42	102.4
Mean:	31.7		19.4	
S.D.+	17.08		11.81	

Number of cigarettes per day	Deceased Cases No.	%	Compeers No.	%
Less than 20	17	8.6	27	22.1
20	61	31.0	43	35.2
More than 20	119	60.4	52	42.6
Total	197	100.0	122	100.0
Mean	31.5		26.4	
S.D.	14.35		13.29	

+ S.D. = Standard deviation.

2066360839

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 23

NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES BY VITAL STATUS, ALL SMOKERS

Number of years smoked	Living			
	Cases		Compeers	
	No.	%	No.	%
1 - 30 yr	6	14.3	21	50.0
31 - 40 yr	23	54.8	14	33.3
41 + yr	13	31.0	7	16.7
Total	42	100.0	42	100.0
Mean:	37.8		29.1	
S.D.‡	7.14		14.53	

Number of years smoked	Deceased			
	Cases		Compeers	
	No.	%	No.	%
1 - 30 yr	46	23.4	36	30.3
31 - 40 yr	74	37.6	48	40.3
41 + yr	77	39.1	35	29.4
Total	197	100.0	119	100.0
Mean:	37.2		33.6	
S.D.	9.44		13.24	

‡ S.D. = Standard deviation.

2063630840

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 24

AGE DISTRIBUTION OF FEMALE LUNG CANCER CASES AND COMPEERS, ALL SMOKERS BY VITAL STATUS.

	LIVING				DECEASED			
	Cases		Compeers		Cases		Compeers	
Age group	No.	%	No.	%	No.	%	No.	%
30 - 54 yr.	12	28.6	19	45.2	52	25.4	28	22.6
55 - 64 yr.	22	52.4	16	38.1	86	42.0	50	40.3
65 + yr.	8	19.0	7	16.7	67	32.7	46	37.1
Total	42	100.0	42	100.0	205	100.0	124	100.0

2063630841

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 25

PACK-YEARS OF CIGARETTES* SMOKED BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS

Pack-years of cigarettes	Living Cases No.	%	Compeers No.	%
1 - 16.42			15	35.7
16.43 - 34.21	10	24.4	13	31.0
34.22 - 43.80	4	9.8	6	14.3
43.81 - 65.70	11	26.8	4	9.5
65.71+	16	39.0	4	9.5
Total	41	100.0	42	100.0

Pack-years of cigarettes	Deceased Cases No.	%	Compeers No.	%
1 - 16.42	8	4.2	17	14.7
16.43 - 34.21	34	17.7	18	15.5
34.22 - 43.80	24	12.5	25	21.6
43.81 - 65.70	51	26.6	39	33.9
65.71+	75	39.1	27	23.3
Total	192	100.0	116	100.0

2063630842

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 26

ODDS RATIOS FOR SMOKING STATUS OF FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS, ALL SMOKERS

Ever smoked cigarettes	CASES No.	%	COMPEERS No.	%	Odds Ratio	95% C.I. Low	High	Chi-square	p Value
Living:									
Yes	42	95.5	42	53.8	18.00	4.07	79.61	20.91	<.001
No	2	4.5	36	46.2					
Total	44	100.0	78	100.0					
Deceased:									
Yes	205	95.3	124	62.0	12.56	6.26	25.20	68.13	<.001
No	10	4.7	76	38.0					
Total	215	100.0	200	100.0					

CURRENT SMOKERS

Ever smoked cigarettes	CASES No.	%	COMPEERS No.	%	Odds Ratio	95% C.I. Low	High	Chi-square	p Value
Living:									
Yes	23	92.0	20	35.7	20.70	4.42	97.07	19.79	<.001
No	2	8.0	36	64.3					
Total	25	100.0	56	100.0					
Deceased:									
Yes	162	94.2	90	54.2	13.68	6.74	27.77	89.05	<.001
No	10	5.8	76	45.8					
Total	172	100.0	166	100.0					

EXSMOKERS

Ever smoked cigarettes	CASES No.	%	COMPEERS No.	%	Odds Ratio	95% C.I. Low	High	Chi-square	p Value
Living:									
Yes	19	90.5	22	37.9	15.55	3.30	73.28	15.01	<.001
No	2	9.5	36	62.1					
Total	21	100.0	58	100.0					
Deceased									
Yes	43	81.1	34	30.9	9.61	4.33	21.35	34.21	<.001
No	10	18.9	76	69.1					
Total	53	100.0	110	100.0					

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 27

ODDS RATIOS FOR AGE FEMALE LUNG CANCER CASES AND COMPERS STARTED TO SMOKE CIGARETTES BY VITAL STATUS, ALL SMOKERS

Age started	CASES No.	%	COMPEERS No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Living:									
Never	2	4.5	76	46.2	1.00				
30+ yr	1	2.3	4	5.1	4.50	.33	61.46	1.48	< 0.05
21 - 29 yr	10	22.7	11	14.1	15.36	3.11	86.20	14.98	< 0.05
19 - 20 yr	6	13.6	7	9.0	15.43	2.57	92.73	12.25	< 0.05
17 - 18 yr	14	31.8	13	16.7	19.38	3.97	97.14	18.46	< 0.05
6 - 16 yr	11	25.0	7	9.0	38.29	5.11	156.46	21.27	< 0.05
Total	44	100.0	78	100.0	17.53*	8.81	34.92	66.62	< 0.05
Deceased:									
Never	10	4.8	76	39.2	1.00				
30+ yr	22	10.5	19	9.8	8.30	3.57	21.66	25.92	< 0.05
21 - 29 yr	37	17.7	22	11.9	12.22	5.28	28.32	40.54	< 0.05
19 - 20 yr	34	16.2	22	11.2	11.75	5.02	27.48	38.21	< 0.05
17 - 18 yr	39	18.7	20	10.2	14.82	6.32	34.73	46.41	< 0.05
6 - 16 yr	67	32.1	34	17.5	14.98	6.38	32.60	57.40	< 0.05
Total	209	100.0	194	100.0	12.57*	8.91	17.75	207.32	< 0.05

* Mantel-Haenszel estimate.
Overall Mantel-Haenszel estimate: 13.36 9.82 18.18 272.92 < 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 29

ODDS RATIOS FOR AGE FEMALE LUNG CANCER CASES AND COMPEERS STOPPED SMOKING CIGARETTES BY VITAL STATUS, ALL SMOKERS

Age Stopped	Cases No.	Cases %	Compeers #	Compeers %	ODDS RATIO	95% C.I. Low	95% C.I. High	CHI-SQUARE	p VALUE
Living: Never smoked	2	9.5	36	62.1	1.00				
19-37yr			6	10.3	1.12	.05	25.19	.01	n.s.
38-50yr	1	4.8	8	13.8	0.25	.18	27.96	.42	n.s.
51-57yr	10	47.6	6	10.3	30.00	5.27	170.12	21.74	< 0.05
58+ yr	8	38.1	2	3.4	72.00	8.78	590.58	26.81	< 0.05
Total	21	100.0	58	100.0	13.84#	6.12	31.29	39.85	< 0.05
Deceased: Never smoked	10	19.2	76	69.1	1.00				
19-37yr	2	3.8	7	6.4	2.17	.40	11.94	.87	n.s.
38-50yr	7	13.5	8	7.3	6.65	1.98	22.30	11.20	< 0.05
51-57yr	11	21.2	9	8.2	9.29	3.09	27.92	19.21	< 0.05
58+ yr	22	42.3	10	9.1	16.72	6.17	45.30	78.59	< 0.05
Total	52	100.0	110	100.0	9.97#	5.29	15.21	66.27	< 0.05
# Mantel-Haenszel estimate. Overall Mantel-Haenszel estimate					10.12	6.50	15.75	105.31	< 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 29

ODDS RATIO FOR USE OF FILTER-TIP CIGARETTES BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS, ALL SMOKERS

Use of filter tip cigarettes	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Living:									
Never smoked	2	4.5	36	46.2	1.00				
Non-Filter	6	13.6	12	15.4	9.00	1.60	50.69	7.86	< 0.05
Both	11	25.0	8	10.3	24.75	4.57	134.17	19.93	< 0.05
Filter	25	56.8	22	28.2	20.45	4.41	94.92	22.27	< 0.05
TOTAL	44	100.0	78	100.0	17.44‡	7.79	39.01	48.41	< 0.05
Deceased:									
Never smoked	10	4.8	76	39.0	1.00				
Non-Filter	41	19.7	26	13.3	11.99	5.27	27.27	41.64	0.05
Both	53	25.5	37	19.0	10.89	4.98	23.79	42.74	< 0.05
Filter	104	50.0	56	28.7	14.11	6.77	29.44	64.08	< 0.05
TOTAL	208	100.0	195	100.0	12.40‡	8.25	18.62	147.54	< 0.05
Overall Mantel-Haenszel estimate:					13.25	9.22	19.03	195.45	< 0.05

‡ Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 30

ODDS RATIOS FOR USUAL USE OF SELF-ROLLED CIGARETTES BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS, ALL SMOKERS

Smoking status	Living: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Living:									
Usually used self-rolled cigarettes	3	60.0	0		102.20	4.05	2579.50	19.97	< 0.05
Never smoked	2	40.0	36	100.0					
TOTAL	5	100.0	36	100.0					

Smoking status	Deceased: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Usually used self-rolled cigarettes	29	74.4	9	10.6	24.49	9.04	66.37	51.15	< 0.05
Never smoked	10	25.6	76	89.4					
TOTAL	39	100.0	85	100.0					
Overall Mantel-Haenszel estimate:					27.48	12.26	61.61	64.72	< 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 31

ODDS RATIOS FOR USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS, ALL SMOKERS.

Number of cigarettes per day	Living Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	2	4.7	36	46.2	1.00				
Less than 20	4	9.3	15	19.2	4.80	.80	29.07	3.35	n.s.
20	15	34.9	17	21.8	15.88	3.26	77.43	16.26	< 0.05
More than 20	22	51.2	10	12.8	39.60	7.93	197.75	31.08	< 0.05
Total	43	100.0	78	100.0	16.61*	7.54	36.57	48.70	< 0.05
Mean among smokers:	31.7		19.4						
S.E.:	17.08		11.81						

Number of cigarettes per day	Deceased Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	10	4.8	75	38.4	1.00				
Less than 20	17	8.2	27	13.8	4.79	1.95	11.72	12.90	< 0.05
20	61	29.5	43	21.7	10.78	5.01	23.20	44.48	< 0.05
More than 20	119	57.5	52	26.3	17.39	8.34	36.29	76.90	< 0.05
Total	207	100.0	198	100.0	10.93*	7.28	16.43	131.84	< 0.05
* Mantel-Haenszel estimate.									
Overall Mantel-Haenszel estimate:					11.89	8.28	17.07	179.88	< 0.05
Mean among smokers:	31.5		26.4						
S.E. S.E.	14.35		13.29						

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 31 (continued)

ODDS RATIOS FOR USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS. CURRENT SMOKERS.

Number of cigarettes per day	Living Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	2	8.3	36	64.3	1.00				
Less than 20	2	8.3	4	7.1	9.00	.98	82.50	4.94	< 0.05
20	7	29.2	9	16.1	14.00	2.47	79.20	12.01	< 0.05
More than 20	13	54.2	7	12.5	33.43	6.14	182.01	24.39	< 0.05
Total	24	100.0	56	100.0	19.00‡	7.66	47.0*	40.41	< 0.05
Mean among smokers:	31.5		22.8						
S.D.	15.61		11.75						

Number of cigarettes per day	Deceased Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	10	6.0	76	45.8	1.00				
Less than 20	10	6.0	16	9.6	4.75	1.70	13.29	9.80	< 0.05
20	45	26.8	32	19.3	10.69	4.80	23.79	39.82	< 0.05
More than 20	103	61.3	42	25.3	18.64	8.80	39.48	75.24	< 0.05
Total	168	100.0	166	100.0	11.33‡	7.56	18.27	124.25	< 0.05
Overall Mantel-Haenszel estimate:					12.74	8.61	18.85	162.37	0.05
Mean among smokers:	32.5		27.7						
S.D.	14.25		12.78						

‡ Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 31 (continued)

ODDS RATIOS FOR USUAL NUMBER OF CIGARETTES SMOKED PER DAY BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS, EXSMOKERS.

Number of cigarettes per day	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	2	9.5	10	31.3	1.00				
Less than 20	2	9.5	11	34.4	.91	.11	7.72	.01	n.s.
20	8	38.1	8	25.0	5.00	.82	30.46	3.32	n.s.
More than 20	9	42.9	3	9.4	15.00	2.02	111.18	8.22	< 0.05
Total	21	100.0	32	100.0	4.35*	1.57	12.05	8.02	< 0.05
Mean among smokers:	22.0		15.5						
S.D.	18.07		11.47						

Number of cigarettes per day	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	10	20.4	76	70.4	1.00				
Less than 20	7	14.3	11	10.2	4.84	1.52	15.34	8.09	< 0.05
20	16	32.7	11	10.2	11.05	4.02	30.41	26.32	< 0.05
More than 20	16	32.7	10	9.3	12.16	4.35	34.03	27.90	< 0.05
Total	49	100.0	108	100.0	9.14*	5.24	15.94	60.84	< 0.05
Overall Mantel-Haenszel estimate:					7.38	4.54	12.00	65.11	< 0.05
Mean among smokers:	26.9		22.0						
S.D.	13.95		14.40						

* Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE XI

ODDS RATIOS FOR NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES, ALL SMOKERS BY VITAL STATUS

Number of years smoked	Living Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	2	4.5	36	46.2	1.00				
1 - 30 yr	6	13.6	21	26.9	5.14	.95	27.83	4.21	< 0.05
31 - 40 yr	23	52.3	14	17.9	29.57	6.14	142.32	27.31	< 0.05
41 + yr	13	29.5	7	9.0	33.43	6.14	182.01	24.39	< 0.05
Total	44	100.0	78	100.0	17.80*	8.18	38.71	52.67	< 0.05
Mean among smokers:	37.8		29.1						
S.D.+	7.14		14.53						

Number of years smoked	Deceased Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	10	4.8	76	39.0	1.00				
1 - 30 yr	46	22.2	36	18.5	9.71	4.41	21.41	37.35	< 0.05
31 - 40 yr	74	35.7	48	24.6	11.72	5.52	24.87	50.36	< 0.05
41 + yr	77	37.2	35	17.9	16.72	7.73	36.15	64.44	< 0.05
Total	207	100.0	195	100.0	12.45*	8.32	18.62	150.68	< 0.05
* Mantel-Haenszel estimate.									
Overall Mantel-Haenszel estimate:					13.35	9.34	19.08	202.42	< 0.05
Mean among smokers:	37.2		33.6						
S.D.	9.44		13.24						

S.D. = Standard deviation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 32 (continued)

ODDS RATIOS FOR NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES, CURRENT SMOKERS BY VITAL STATUS

Number of years smoked	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	2	8.0	36	64.3	1.00				
1 - 30 yr	4	16.0	4	7.1	18.00	2.47	131.29	11.66	< 0.05
31 - 40 yr	12	48.0	10	17.9	21.60	4.14	112.79	18.92	< 0.05
41 + yr	7	28.0	6	10.7	21.00	3.49	126.22	15.73	< 0.05
Total	25	100.0	56	100.0	20.57*	9.46	49.97	44.56	< 0.05
Mean among smokers:	37.7		37.5						
S.D.	7.52		10.38						

Number of years smoked	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	10	6.0	76	46.6	1.00				
1 - 30 yr	32	19.2	20	12.3	12.16	5.12	28.86	38.13	< 0.05
31 - 40 yr	62	37.1	37	22.7	12.74	5.87	27.64	50.35	< 0.05
41 + yr	63	37.7	30	18.4	15.96	7.25	35.16	58.26	< 0.05
Total	167	100.0	163	100.0	13.63*	20.83	8.92	145.62	< 0.05
Mean among smokers:	37.5		36.4						
S.D.	9.05		11.49						

* Mantel-Haenszel estimate.
Overall Mantel-Haenszel estimate: 14.51 9.89 21.27 187.47 < 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 32 (continued)

ODDS RATIOS FOR NUMBER OF YEARS FEMALE LUNG CANCER CASES AND COMPEERS SMOKED CIGARETTES, EXSMOKERS BY VITAL STATUS

Number of years smoked	Living Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	2	9.5	36	62.1	1.00				
1 - 30 yr	2	9.5	17	29.3	2.12	.27	16.34	.54	n.s.
31 - 40 yr	11	52.4	4	6.9	49.50	7.97	307.59	26.92	< 0.05
41 + yr	6	28.6	1	1.7	198.00	8.42	1385.03	26.17	< 0.05
Total	21	100.0	58	100.0	17.09*	7.34	39.83	43.25	< 0.05
Mean among smokers:	38.0		21.5						
S.D.	6.58		13.63						

Number of years smoked	Deceased Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never smoked	10	20.0	76	70.4	1.00				
1 - 30 yr	14	28.0	16	14.8	6.65	2.51	17.62	14.64	< 0.05
31 - 40 yr	12	24.0	11	10.2	8.29	2.90	23.71	18.52	< 0.05
41 + yr	14	28.0	5	4.6	21.28	6.31	71.76	33.99	< 0.05
Total	50	100.0	108	100.0	9.66*	5.58	16.73	65.46	< 0.05
* Mantel-Haenszel estimate. Overall Mantel-Haenszel estimate:					11.27	7.12	17.83	107.18	< 0.05
Mean among smokers:	35.4		25.8						
S.D.	12.22		14.68						

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE II

ODDS RATIOS FOR PACK-YEARS† OF CIGARETTES SMOKED BY FEMALE LUNG CANCER CASES AND COMPEERS BY VITAL STATUS

Pack-years of cigarettes	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	2	4.7	36	46.2	1.00				
1 - 16.42			15	19.2	.47	.02	10.29	.24	n.s.
16.43 - 34.21	10	23.3	13	16.7	13.85	2.67	71.75	13.24	< 0.05
34.22 - 43.80	4	9.3	6	7.7	12.00	1.79	80.61	8.77	< 0.05
43.81 - 65.70	11	25.6	4	5.1	49.50	7.97	307.59	26.92	< 0.05
65.71+	16	37.2	4	5.1	72.00	11.94	434.17	34.20	< 0.05
Total	43	100.0	78	100.0	15.95††	8.41	30.26	71.94	< 0.05

Pack-years of cigarettes	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never smoked	10	5.0	76	39.6	1.00				
1 - 16.42	8	4.0	17	8.9	2.58	1.23	10.41	5.92	< 0.05
16.43 - 34.21	34	16.8	18	9.4	14.36	6.90	34.35	42.12	0.05
34.22 - 43.80	24	11.9	25	13.0	7.30	3.07	17.33	23.11	< 0.05
43.81 - 65.70	51	25.2	29	15.1	13.37	6.90	29.90	48.44	< 0.05
65.71+	75	37.1	27	14.1	21.11	9.56	46.64	72.18	< 0.05
Total	202	100.0	192	100.0	11.51††	8.18	15.47	199.58	0.05
Overall Mantel-Haenszel estimate:					12.27	9.10	16.82	257.79	< 0.05

† Pack-years = number of packs (20 cigarettes/pack) X number years smoked.
†† Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 34

STATE OF BIRTH OF FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

State of birth	Cases						Compeers					
	All		Smoked		Never Smoked		All		Smoked		Never Smoked	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Texas	142	100.0	137	96.5	5	3.5	147	100.0	77	52.4	70	47.6
Other	117	100.0	110	94.0	7	6.0	131	100.0	89	67.9	42	32.1
Total	259		247		12		278		166		112	

COUNTY OF BIRTH OF FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

County of birth	Cases						Compeers					
	All		Smoked		Never Smoked		All		Smoked		Never Smoked	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Harris	25	100.0	24	96.0	1	4.0	29	100.0	17	58.6	12	41.4
Other	234	100.0	223	95.3	11	4.7	249	100.0	149	59.8	100	40.2
Total	259		247		12		278		166		112	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 25

ODDS RATIOS FOR RELIGIOUS PREFERENCE OF FEMALE LUNG CANCER CASES AND COMPEERS PRIOR TO 16 YEARS OF AGE BY SMOKING STATUS

Religious preference prior to 16 yr. age	Smoked cigarettes Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-square	p Value
Protestant	203	88.6	119	76.8	2.76	1.36	5.11	8.42	<0.05
Catholic	26	11.4	36	23.2					
Total	229	100.0	155	100.0					

Religious preference prior to 16 yr. age	Never smoked cigarettes Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-square	p Value
Protestant	8	80.0	87	82.1	.87	.17	4.45	.02	n.s.
Catholic	2	20.0	19	17.9					
Total	10	100.0	106	100.0					
Mantel-Haenszel odds ratio :					2.12	1.28	3.50	8.76	<0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 36

HIGHEST GRADE IN SCHOOL ATTAINED BY FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS.

School grade attained	ALL				CASES				COMPEERS			
	Smoked		Never Smoked		Smoked		Never Smoked		Smoked		Nev Smo	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	
0 - 12	279	69.6	86	72.3	164	68.0	6	54.5	115	71.9	80	
13 - 17	122	30.4	33	27.7	77	32.0	5	45.5	45	28.1	28	
Total	401	100.0	119	100.0	241	100.0	11	100.0	160	100.0	108	

Unknown: Cases = 7, Compeers = 10.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 37

ODDS RATIOS FOR MARITAL STATUS OF FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

Smoked cigarettes

Marital status	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Not married*	118	47.8	56	33.7	1.80	1.20	2.70	8.02	< 0.05
Married	129	52.2	110	66.3					
Total	247	100.0	166	100.0					

Never smoked cigarettes

Marital status	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Not married	4	33.3	47	42.0	.69	.20	2.43	.33	n.s.
Married	8	66.7	65	58.0					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio estimate:					1.63	1.11	2.40	6.28	< 0.05

* Not married: Widowed, Divorced, Separated, Never married.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 3B

USUAL OCCUPATION OF FEMALE LUNG CANCER CASES AND COMPEERS
DETERMINED BY LONGEST DURATION EMPLOYED AND AS REPORTED BY RESPONDENTS.

CATEGORIES OF OCCUPATIONS	Cases: Longest Duration No.	%	Cases: Reported by Respondent No.	%	Compeers: Longest Duration No.	%	Compeers: Reported by Respondent No.	%
Professional, Technical, and Managerial (001-199)	31	12.8	37	14.5	25	9.3	32	11.5
Clerical and Sales (201-299)	32	13.2	51	19.9	42	15.6	46	16.7
Service (301-389)*	175	72.3	160	62.5	192	71.4	190	69.1
Agricultural, Fishery, Forestry and related (401-461)			1	.4	1	.4	1	.4
Processing (500-599)					1	.4		
Machine Trades (600-699)					1	.4	1	.4
Benchwork (700-795)			3	1.2	5	1.9	3	1.1
Structural Work (800-899)	1	.4	1	.4	1	.4		
Miscellaneous (900-979)	3	1.2	3	1.2	1	.4	2	.7
Total	242	100.0	256	100.0	269	100.0	275	100.0
Unemployed, retired, disabled, on welfare, or information too vague:	15				9		3	
Occupation not known:	2		2					
Invalid responses:			1				1	
Total	259		259		278		278	

Percent of cases and compeers with Housewife as a usual occupation within the Service category and among all occupations.

Method of obtaining information	No.	% Servic	% all occupations
Longest duration:			
Cases	149	85.1	61.6
Compeers	177	92.2	65.8
Reported by respondent:			
Cases	135	84.4	52.7
Compeers	174	91.6	63.3

Housewife comprised the majority of usual occupations in the Service category and one-half to two-thirds of all usual occupations.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 39

USUAL OCCUPATION OF FEMALE LUNG CANCER CASES AND COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED BY AGE

CATEGORIES OF OCCUPATIONS	30-39 yr. Cases No.	30-39 yr. Cases %	30-39 yr. Compeers No.	30-39 yr. Compeers %	40-49 yr. Cases No.	40-49 yr. Cases %	40-49 yr. Compeers No.	40-49 yr. Compeers %
Professional, Technical, and Managerial (001-199)					4	17.4	3	11.5
Clerical and Sales (201-299)			1	25.0	3	13.0	4	15.4
Service (301-389)*	2	100.0	3	75.0	15	65.2	19	73.1
Agricultural, Fishery, Forestry and related (401-461)								
Processing (500-599)								
Machine Trades (600-699)								
Benchwork (700-795)								
Structural Work (800-899)								
Miscellaneous (900-979)					1	4.3		
Total	2	100.0	4	100.0	23	100.0	26	100.0

CATEGORIES OF OCCUPATIONS	50-59 yr Cases No.	50-59 yr Cases %	50-59 yr Compeers No.	50-59 yr Compeers %	60-69 yr Cases No.	60-69 yr Cases %	60-69 yr Compeers No.	60-69 yr Compeers %	70+ yr Cases No.	70+ yr Cases %	70+ yr Compeers No.	70+ yr Compeers %
Professional, Technical, and Managerial (001-199)	6	7.3	12	14.0	18	19.1	9	8.5	3	7.30	1	2.13
Clerical and Sales (201-299)	13	15.9	10	11.6	11	11.7	16	15.1	5	12.20	11	23.40
Service (301-389)*	63	76.8	62	72.1	62	66.0	74	69.8	33	80.50	34	72.34
Agricultural, Fishery, Forestry and related (401-461)			1	1.2								
Processing (500-599)							1	.9				
Machine Trades (600-699)							1	.9				
Benchwork (700-795)			1	1.2			3	2.8			1	2.13
Structural Work (800-899)					1	1.1	1	.9				
Miscellaneous (900-979)					2	2.1	1	.9				
Total	82	100.0	86	100.0	94	100.0	106	100.0	41	100.00	47	100.00

*Age groups estimated by subtracting dates of birth from 1 January, 1979.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 29 (continued)

USUAL OCCUPATION OF FEMALE LUNG CANCER CASES AND COMPEERS REPORTED BY RESPONDENTS BY AGE GROUPS*.

CATEGORIES OF OCCUPATIONS	30-39 yr Cases No.	30-39 yr Cases %	30-39 yr Compeers No.	30-39 yr Compeers %	40-49 yr Cases No.	40-49 yr Cases %	40-49 yr Compeers No.	40-49 yr Compeers %
Professional, Technical, and Managerial (001-199)			1	25.0	3	13.6	4	14.3
Clerical and Sales (201-299)			1	25.0	5	22.7	3	10.7
Service (301-389)	2	100.0	2	50.0	13	59.1	21	75.0
Agricultural, Fishery, Forestry and related (401-461)								
Processing (500-599)								
Machine Trades (600-699)								
Benchwork (700-795)								
Structural Work (800-899)								
Miscellaneous (900-979)					1	4.5		
Total	2	100.0	4	100.0	22	100.0	28	100.0

CATEGORIES OF OCCUPATIONS	50-59 yr Cases No.	50-59 yr Cases %	50-59 yr Compeers No.	50-59 yr Compeers %	60-69 yr Cases No.	60-69 yr Cases %	60-69 yr Compeers No.	60-69 yr Compeers %	70+ yr Cases No.	70+ yr Cases %	70+ yr Compeers No.	70+ yr Compeers %
Professional, Technical, and Managerial (001-199)	15	16.5	18	20.2	14	14.4	7	6.5	5	11.36	2	4.26
Clerical and Sales (201-299)	22	24.2	13	14.6	19	19.6	19	17.8	8	11.36	10	21.28
Service (301-389)	50	54.9	56	62.9	62	63.9	77	72.0	33	75.00	34	72.34
Agricultural, Fishery, Forestry and related (401-461)	1	1.1	1	1.1								
Processing (500-599)												
Machine Trades (600-699)							1	.9				
Benchwork (700-795)	3	3.3					2	1.9			1	2.13
Structural Work (800-899)									1	2.27		
Miscellaneous (900-979)			1	1.1	2	2.1	1	.9				
Total	91	100.0	89	100.0	97	100.0	107	100.0	44	100.00	47	100.00

*Age groups estimated by subtracting dates of birth from 1 January, 1979.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 40

USUAL OCCUPATION OF FEMALE LUNG CANCER CASES DETERMINED BY LONGEST DURATION EMPLOYED AND AS REPORTED BY RESPONDENTS BY VITAL STATUS.

CATEGORIES OF OCCUPATIONS	CASES, LIVING				CASES, DECEASED			
	Longest duration employed		Reported by respondent		Longest duration employed		Reported by respondent	
	No.	%	No.	%	No.	%	No.	%
Professional, Technical, and Managerial (001-199)	4	10.0	8	18.2	27	13.4	29	13.7
Clerical and Sales (201-299)	6	15.0	9	20.5	26	12.9	42	19.8
Service (301-389)*	30	75.0	26	59.1	145	71.8	134	63.2
Agricultural, Fishery, Forestry and related (401-461)			1	2.3				
Processing (500-599)								
Machine Trades (600-699)								
Benchwork (700-795)							1	
Structural Work (800-899)					1	.5	1	.5
Miscellaneous (900-979)					3	1.5	3	1.4
Total	40	100.0	44	100.0	202	100.0	212	100.0
*Service includes Housewives:	27		23		121		112	
% of Service occupations		90.0		88.5		83.4		83.6
% of all occupations		67.5		52.3		59.9		52.8
Unemployed, retired, disabled, on welfare, or too vague to code:	4				11			
Occupations unknown:					2		2	
Invalid response:							1	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 40 (continued)

USUAL OCCUPATION OF COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED AND AS REPORTED BY RESPONDENTS BY VITAL STATUS.

CATEGORIES OF OCCUPATIONS	COMPEERS, LIVING: Longest duration employed No.	%	COMPEERS, LIVING: Reported by respondent No.	%	COMPEERS, DECEASED: Longest duration employed No.	%	COMPEERS, DECEASED: Reported by respondent No.	%
Professional, Technical, and Managerial (001-199)	15	19.5	14	17.9	10	5.2	18	9.1
Clerical and Sales (201-299)	11	14.3	13	16.7	31	16.1	33	16.8
Service (301-389)*	50	64.9	50	64.1	142	74.0	140	71.1
Agricultural, Fishery, Forestry and related (401-461)					1	.5	1	.5
Processing (500-599)					1	.5		
Machine Trades (600-699)					1	.5	1	.5
Benchwork (700-799)	1	1.3			4	2.1	3	1.5
Structural Work (800-899)					1	.5		
Miscellaneous (900-979)			1	1.3	1	.5	1	.5
Total	77	100.0	78	100.0	192	100.0	197	100.0
*Service includes Housewives:	48		47		129		127	
% of Service occupations		96.0		94.0		90.8		90.7
% of all occupations		62.3		60.3		67.2		64.5
Unemployed, retired, disable, on welfare, or too vague to code:	1				8		2	
Occupations unknown:								
Invalid responses:							1	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 41

USUAL OCCUPATION OF FEMALE LUNG CANCER CASES AND COMPEERS
DETERMINED BY LONGEST DURATION EMPLOYED BY SMOKING STATUS

CATEGORIES OF OCCUPATIONS	Cases All No.	Cases Smokers No.	Cases Smokers %	Compeers All No.	Compeers Smokers No.	Compeers Smokers %
Professional, Technical, and Managerial (001-199)	31	28	90.3	25	17	68.0
Clerical and Sales (201-299)	32	32	100.0	42	23	54.8
Service (301-389)‡	175	166	94.9	192	114	59.4
Agricultural, Fishery, Forestry and related (401-461)				1	1	100.0
Processing (500-599)				1	1	100.0
Machine Trades (600-699)				1		
Benchwork (700-795)				5	2	40.0
Structural Work (800-899)	1	1	100.0	1	1	100.0
Miscellaneous (900-979)	3	3	100.0	1	1	100.0
Total	242	230	95.0	269	160	59.5
Unemployed,retired,disabled,on welfare, or information vague:	15			9		
Unknown:	2					

‡Includes Housewife:
Cases = 140 (84.3%), Compeers = 102 (89.5%).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 42

USUAL INDUSTRY OF FEMALE LUNG CANCER CASES AND COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED.

CATEGORY OF INDUSTRY	Cases No.	Cases %	Compeers No.	Compeers %
Agricultural, Forestry, and Fishing (0001-0971)			1	.7
Mining (1000-0971)	3	2.0		
Construction (1500-1799)	3	2.0		
Manufacturing (2000-3999)	17	11.1	17	12.3
Transportation and Public Utilities (4000-4971)	2	1.3	8	5.8
Wholesale Trade (5000-5199)	3	2.0	6	4.3
Retail Trade (5200-5999)	40	26.1	34	24.6
Finance, Insurance, and Real Estate (6000-6799)	18	11.8	11	8.0
Services (7000-8999)	60	39.2	55	39.9
Public Administration (9100-9721)	7	4.6	6	4.3
Total	153	100.0	138	100.0
	No.	% of Total	No.	% of Total
Unemployed, retired, disabled, or on welfare:	103	40.2	139	50.2
Unknown:	3		1	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 43

USUAL INDUSTRY OF FEMALE LUNG CANCER CASES AND COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED, BY AGE

CATEGORIES OF INDUSTRIES	30-39 years Cases No.	30-39 years Cases %	30-39 years Compeers No.	30-39 years Compeers %	40-49 years Cases No.	40-49 years Cases %	40-49 years Compeers No.	40-49 years Compeers %
Agriculture, Forestry, and Fishing (0100-0971)								
Mining (1000-1499)								
Construction (1500-1799)								
Manufacturing (2000-3999)	1	50.0			4	25.0		
Transportation, Communications, Electric, Gas, and Sanitary Services (4000-4971)					1	6.3	2	16.7
Wholesale Trade (5000-5199)			1	50.0				
Retail Trade (5200-5299)					5	31.3	4	33.3
Finance, Insurance and Real Estate (6000-6799)					3	18.8		
Services (7000-8999)	1	50.0	1	50.0	3	18.8	5	41.7
Public Administration (9100-9721)							1	8.3
Total	2	100.0	2		16	100.0	12	100.0

CATEGORIES OF INDUSTRIES	50-59 years Cases No.	50-59 years Cases %	50-59 years Compeers No.	50-59 years Compeers %	60-69 years Cases No.	60-69 years Cases %	60-69 years Compeers No.	60-69 years Compeers %	70 or more years Cases No.	70 or more years Cases %	70 or more years Compeers No.	70 or more years Compeers %
Agriculture, Forestry, and Fishing (0100-0971)			1	1.9								
Mining (1000-1499)					3	4.8						
Construction (1500-1799)	3	5.0										
Manufacturing (2000-3999)	4	6.7	7	13.2	8	12.9	8	15.7			2	10.0
Transportation, Communications, Electric, Gas, and Sanitary Services (4000-4971)			4	7.5	1	1.6	2	3.9				
Wholesale Trade (5000-5199)	1	1.7	2	3.8	1	1.6	2	3.9	1	7.7	1	5.0
Retail Trade (5200-5299)	16	26.7	11	20.8	16	25.8	15	29.4	3	23.1	4	20.0
Finance, Insurance and Real Estate (6000-6799)	6	10.0	6	11.3	7	11.3	3	5.9	2	15.4	2	10.0
Services (7000-8999)	25	41.7	21	39.6	24	38.7	19	37.3	7	53.8	9	45.0
Public Administration (9100-9721	5	8.3	1	1.9	2	3.2	2	3.9			2	10.0
Total	60	100.0	53	100.0	62	100.0	51	100.0	13	100.0	20	100.0

	Cases	Compeers
Unemployed, Housewife, retired	103	139
Unknown:	3	1

*Age groups estimated by subtracting dates of birth from 1 January, 1979.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 44

USUAL INDUSTRY OF FEMALE LUNG CANCER CASES AND COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED BY VITAL STATUS

CATEGORIES OF INDUSTRIES	Cases				Compeers			
	Alive		Deceased		Alive		Deceased	
	No.	%	No.	%	No.	%	No.	%
Agriculture, Forestry, and Fishing (0100-0971)							1	1.1
Mining (1000-1499)	1	4.0	2	1.6				
Construction (1500-1799)	1	4.0	2	1.6				
Manufacturing (2000-3999)	3	12.0	14	10.9	9	17.6	8	8.2
Transportation, Communications, Gas, and Electric Services (4000-4971)			2	1.6	2	3.9	6	6.9
Wholesale Trade (5000-5199)			3	2.3			6	6.9
Retail Trade (5200-5299)	9	32.0	32	25.0	12	23.5	22	25.3
Finance, Insurance, and Real Estate (6000-6799)	2	8.0	16	12.5	4	7.8	7	8.0
Services (7000-8999)	8	32.0	52	40.6	21	41.2	34	39.1
Public Administration (9100-9721	2	8.0	5	3.9	3	5.9	3	3.4
Total	25	100.0	128	100.0	51	100.0	87	100.0
Not in Labor Force:	19		84		27		112	
Unknown:			3				1	
Total			259				278	

2063630867

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 45

USUAL INDUSTRY OF FEMALE LUNG CANCER CASES AND COMPEERS DETERMINED BY LONGEST DURATION EMPLOYED AMONG SMOKERS

CATEGORIES OF INDUSTRIES	Cases No.	Cases %	Compeers No.	Compeers %
Agriculture, Forestry, and Fishing (0100-0971)			1	100.0
Mining (1000-1499)	3	100.0		
Construction (1500-1799)	3	100.0		
Manufacturing (2000-3999)	17	100.0	10	58.8
Transportation, Communications, Electric, Gas and Sanitary Services (4000-4971)	2	100.0	3	37.5
Wholesale Trade (5000-5199)	3	100.0	2	33.3
Retail Trade (5200-5299)	39	97.5	24	70.6
Finance, Insurance, and Real Estate (6000-6799)	13	100.0	10	90.9
Services (7000-8999)	57	95.0	35	63.6
Public Administration (9100-9721	7	100.0	3	50.0
Total	149	97.4	88	63.8
Not in labor force:	95		76	

2063630868

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 46

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION AND BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No	Compeers %	Odds Ratio	95%C.I. Low	95%C.I. High	Chi-Square	p Value
Yes	164	63.3	161	57.9	1.25	.89	1.78	1.64	n.s.
No	95	36.7	117	42.1					
Total	259	100.0	278	100.0					

SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No	Compeers %	Odds Ratio	95%C.I. Low	95%C.I. High	Chi-Square	p Value
Smokers:									
Yes	161	65.2	102	61.4	1.17	.78	1.77	.69	n.s.
No	86	34.8	64	38.6					
Total	247	100.0	166	100.0					
Nonsmokers:									
Yes	3	25.0	59	52.7	.3	.08	1.16	3.32	n.s.
No	9	75.0	53	47.3					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.03	.70	1.51	.02	n.s.

n.s. = not significant at the 5% level.

2063630869

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 47

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION BY AGE

Age groups*	Employed	Cases	Compeers	Odds Ratio	95% Confidence interval Low	High	Chi-Square	p Value
30-39 yrs.	Yes	1	2	1.00	.03	29.81	.01	n.s.
	No	1	2					
40-44 yrs.	Yes	4	2	1.00	.05	18.92	.01	n.s.
	No	2	1					
45-49 yrs.	Yes	9	18	.44	.12	1.60	1.60	n.s.
	No	9	7					
50-54 yrs.	Yes	28	28	.92	.35	2.42	.03	n.s.
	No	12	11					
55-59 yrs.	Yes	41	32	2.33	.98	5.55	3.71	n.s.
	No	11	20					
60-64 yrs.	Yes	38	31	1.06	.49	2.30	.02	n.s.
	No	22	19					
65-69 yrs.	Yes	22	29	1.33	.58	3.04	.45	n.s.
	No	16	28					
70 + yrs.	Yes	21	19	1.39	.61	3.19	.62	n.s.
	No	23	29					
Total	Yes	164	161	1.22††	.85	1.74	1.19	n.s.
	No	95	117					

*Age calculated by subtracting date of birth from the 1 January, 1979.

†† Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 48

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION BY AGE AND SMOKING STATUS

Age groups‡	Ever employed in a high risk occupation or industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked										
30 - 49 yr	Yes	14	58.3	13	61.9	.86	.26	2.85	.06	n.s.
	No	10	41.7	8	38.1					
50 - 59 yr	Yes	69	75.0	37	63.8	1.70	.83	3.48	2.16	n.s.
	No	23	25.0	21	36.2					
60 - 69 yr	Yes	59	65.6	43	62.3	1.15	.60	2.21	.18	n.s.
	No	31	34.4	26	37.7					
70 + yr	Yes	19	46.3	9	50.0	.86	.29	2.62	.07	n.s.
	No	22	53.7	9	50.0					
Total	Yes	161	65.2	102	61.4	1.22‡	.80	1.84	.96	n.s.
	No	86	34.8	64	38.6					
Never smoked										
30 - 49 yr	Yes			9	81.8	.09	.01	2.88	2.46	n.s.
	No	1	100.0	2	18.2					
50 - 59 yr	Yes			23	69.7	.45	.01	24.08	.16	n.s.
	No			10	30.3					
60 - 69 yr	Yes	1		17	44.7	.18	.02	1.58	2.88	n.s.
	No	7	87.5	21	55.3					
70 + yr	Yes	2		10	33.3	4.00	.32	49.60	1.31	n.s.
	No	1	33.3	20	66.7					
Total	Yes	3		59	52.7	.45‡	.14	1.40	1.91	n.s.
	No	9	75.0	53	47.3					
OVERALL MANTEL-HAENSZEL ESTIMATE‡						1.08	.74	1.59	.17	n.s.

‡ Mantel-Haenszel estimate.

‡‡ n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 49

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION BY PACK-YEARS OF CIGARETTES SMOKED

Age groups‡	Pack-years smoked	Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
30 - 54 yr.	1 - 34.21	Yes	9	47.37	15	57.69	.66	.20	2.17	.47	n.s.
		No	10	52.63	11	42.31					
	34.22 - 65.70	Yes	18	72.00	12	80.00	.64	.14	2.99	.32	n.s.
		No	7	28.00	3	20.00					
	65.71 +	Yes	12	75.00	3	50.00	3.00	.42	21.39	1.26	n.s.
		No	4	25.00	3	50.00					
55 - 64 yr.	1 - 34.21	Yes	16	69.57	11	64.71	1.25	.33	4.73	.11	n.s.
		No	7	30.43	6	35.29					
	34.22 - 65.70	Yes	32	76.19	17	62.96	1.88	.66	5.41	1.40	n.s.
		No	10	23.81	10	37.04					
	65.71 +	Yes	29	70.73	12	66.67	1.21	.37	4.00	.10	n.s.
		No	12	29.27	6	33.33					
65 + yr.	1 - 34.21	Yes	4	40.00	13	65.00	.36	.08	1.71	1.70	n.s.
		No	6	60.00	7	35.00					
	34.22 - 65.70	Yes	14	60.87	12	54.55	1.30	.40	4.24	.18	n.s.
		No	9	39.13	10	45.45					
	65.71 +	Yes	16	47.06	4	57.14	.67	.13	3.44	.24	n.s.
		No	18	52.94	3	42.86					
OVERALL MANTEL-HAENSZEL		Yes	150	26.28	99	19.18	1.04	.67	1.61	.03	n.s.
		No	83	57.31	59	80.82					
Never smoked:			12		112						
Unknown duration smoked:			14		7						
Total:			259		277						

‡ Age estimated by subtracting date of birth from 1 January, 1979.
††n.s. = Not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 50

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	150	57.9	142	51.1	1.32	.94	1.85	2.57	n.s.*
No	109	42.1	136	48.9					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smokers:									
Yes	147	59.5	92	55.4	1.18	.79	1.75	.69	n.s.
No	100	40.5	74	44.6					
Total	247	100.0	166	100.0					
Nonsmokers:									
Yes	3	25.0	50	44.6	.41	.11	1.61	1.71	n.s.
No	9	75.0	62	55.4					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.07	.74	1.57	.14	n.s.

* n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 51

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND CONTROLS IN A HIGH RISK INDUSTRY BY AGE

Age Groups (5 Years)*	Employed	Cases No.	Cases %	Controls No.	Controls %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
30-34 yrs.	Yes	0		0		5.00	.04	711.90	.44	n.s.††
	No	0		2	100.00					
35-39 yrs.	Yes	1	50.00	2	100.00	.20	.01	8.83	.75	n.s.
	No	1	50.00	0	.00					
40-44 yrs.	Yes	4	66.67	2	66.67	1.00	.05	18.92	.01	n.s.
	No	2	33.33	1	33.33					
45-49 yrs.	Yes	9	52.94	12	52.00	1.04	.30	3.57	.01	n.s.
	No	8	47.06	12	48.00					
50-54 yrs.	Yes	27	67.50	26	66.67	1.04	.41	2.65	.01	n.s.
	No	13	32.50	13	33.33					
55-59 yrs.	Yes	39	75.00	29	53.85	2.57	1.12	5.91	5.08	< 0.05
	No	13	25.00	24	46.15					
60-64 yrs.	Yes	32	50.32	25	50.00	1.14	.54	2.42	.12	n.s.
	No	28	46.67	25	50.00					
65-69 yrs.	Yes	19	50.00	28	49.12	1.04	.46	2.35	.01	n.s.
	No	19	50.00	29	50.88					
70-74 yrs.	Yes	14	43.75	10	37.04	1.32	.46	3.77	.27	n.s.
	No	18	56.25	17	62.96					
75-79+ yrs.	Yes	5	41.67	8	38.10	1.16	.27	4.93	.04	n.s.
	No	7	58.33	13	61.90					
Total	Yes	150	57.92	142	51.08	1.28	.90	1.81	1.97	n.s.
	No	109	42.08	136	48.92					

*Age calculated by subtracting date of birth from 1 January, 1979.

†† Mantel - Haenszel estimate.

2063630874

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 52

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY AGE AND SMOKING STATUS

Age groups	Ever employed in a high risk industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked										
30 - 49 yr	Yes	14	58.3	10	47.6	1.54	.47	5.01	.52	n.s.
	No	10	41.7	11	52.4					
50 - 59 yr	Yes	66	71.7	34	58.6	1.79	.90	3.58	2.75	n.s.
	No	26	28.3	24	41.4					
60 - 69 yr	Yes	50	55.6	39	56.5	.96	.51	1.81	.01	n.s.
	No	40	44.4	30	43.5					
70 + yr	Yes	17	41.5	9	50.0	.71	.23	2.16	1.66	n.s.
	No	24	58.5	9	50.0					
Total	Yes	147	59.5	92	55.4	1.20*	.81	1.80	.87	n.s.
	No	100	40.5	74	44.6					
Never smoked										
30 - 49 yr	Yes			7	63.6	.20	.01	5.04	.98	n.s.
	No	1	100.0	4	36.4					
50 - 59 yr	Yes			20	60.6	.66	.01	35.22	.04	n.s.
	No			13	39.4					
60 - 69 yr	Yes	1		14	36.8	.24	.03	2.20	1.79	n.s.
	No	7	87.5	24	63.2					
70 + yr	Yes	2		9	30.0	4.67	.37	58.29	1.65	n.s.
	No	1	33.3	21	70.0					
Total	Yes	3		50	44.6	.61*	.19	2.01	.65	n.s.
	No	9	75.0	62	55.4					
OVERALL MANTEL-HAENSZEL ESTIMATE:						1.12	.77	1.64	.36	n.s.

Mantel-Haenszel estimate.
** n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 53

FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY

Frequency of employment	Cases No.	Cases %	Compeers No.	Compeers %
1	58	38.7	67	47.2
2	45	30.0	32	22.5
3	20	13.3	22	15.5
4	11	7.3	12	8.5
5	9	6.0	5	3.5
6	6	4.0	2	1.4
7	1	.7	2	1.4
Total	150	100.0	142	100.0
Mean:	2.27		2.08	
S.D.:	1.45		1.37	

S.D. = Standard deviation.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 54

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY

Frequency of employment	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	109	42.1	136	48.9	1.00				
1	58	22.4	67	24.1	1.08	.70	1.66	.12	n.s.
2	45	17.4	32	11.5	1.75	1.04	2.95	4.57	< 0.05
3	20	7.7	22	7.9	1.13	.59	2.19	.14	n.s.
4	11	4.2	12	4.3	1.14	.49	2.69	.09	n.s.
5	9	3.5	5	1.8	2.25	.73	6.90	2.09	n.s.
6	6	2.3	2	.7	3.74	.74	18.92	2.91	n.s.
7	1	.4	2	.7	.52	.06	6.97	.15	n.s.
Total	259	100.0	278	100.0	1.34††	1.03	1.74	4.77	< 0.05

† n.s. = not significant at the 5% level.
†† Mantel-Haenszel estimate:

Mean times employed:	2.27	2.08
Standard deviation	1.45	1.37

2063630877

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 55

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY AGE

Frequency of employment	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
35 - 49 years									
Never	11	44.00	13	43.33	1.00				
1	4	16.00	9	30.00	.53	.13	2.18	.79	n.s.
2 - 7	10	40.00	8	26.67	1.48	.43	5.05	.39	n.s.
Total	25	100.00	30	100.00	.94	.28	3.27	.02	n.s.
50 - 59 years									
Never	26	28.26	37	40.66	1.00				
1	24	26.09	24	26.37	1.42	.67	3.03	.84	n.s.
2-7	42	45.65	30	32.97	1.99	1.00	3.96	3.91	< 0.05
Total	92	100.00	91	100.00	1.71	1.03	2.84	4.31	< 0.05
60 - 69 years									
Never	47	47.96	54	50.47	1.00				
1	22	22.47	24	22.43	1.10	.55	2.20	.07	n.s.
2-7	28	28.57	29	27.10	1.11	.58	2.13	.10	n.s.
Total	98	100.00	107	100.00	1.11	.69	1.78	.17	n.s.
70 or more years									
Never	25	56.82	30	62.50	1.00				
1	7	15.91	10	20.83	.84	.29	2.53	.10	n.s.
2-7	12	27.27	8	16.67	1.80	.64	5.09	1.24	n.s.
Total	44	100.00	48	100.00	1.26	.60	2.66	.36	n.s.
MANTEL-HAENSZEL:					1.29	.96	1.73	2.81	n.s.

Never employed 30 to 34 years of age: Compeers = 2.

2063630878

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 56

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY SMOKING STATUS

Frequency of employment	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Never	100	40.5	74	44.6	1.00				
1	57	23.1	48	28.9	.88	.54	1.43	.27	n.s.
2	44	17.8	19	11.4	1.71	.93	3.17	2.97	n.s.
3	19	7.7	12	7.2	1.17	.54	2.56	.16	n.s.
4	11	4.5	7	4.2	1.16	.43	3.14	.09	n.s.
5	9	3.6	4	2.4	1.67	.49	5.61	.69	n.s.
6	6	2.4	1	.6	4.44	.52	37.67	2.21	n.s.
7	1	.4	1	.6	.74	.05	12.03	.05	n.s.
Total	247	100.0	166	100.0	1.22‡	.90	1.66	1.65	n.s.
Never smoked cigarettes									
Never	9	75.0	62	55.4	1.00				
Employed: More than once	2	16.7	31	27.7	.44	.09	2.18	1.04	n.s.
Once	1	8.3	19	17.0	.36	.04	3.05	.94	n.s.
Total	12	100.0	112	100.0	.41‡	.12	1.43	1.96	n.s.
Overall Mantel-Haenszel estimate:					1.13	.84	1.52	.70	n.s.

‡ Mantel-Haenszel estimate.

2063630879

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 57

DURATION OF EMPLOYMENT OF FEMALE
LUNG CANCER CASES AND CONTROLS
IN A HIGH RISK INDUSTRY

Number of years employed	Cases No.	%	Controls No.	%
1 - 5	67	47.5	78	55.6
6 - 10	22	15.6	16	13.3
11 - 15	20	14.2	6	4.4
16 +	32	22.7	26	19.3
Total	141	100.0	135	100.0
Unknown:	9		7	
Mean:	10.3		8.7	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 38

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY

Number of years employed	Cases No	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	109	43.6	136	50.2	1.00				
1 - 5	67	26.8	75	27.7	1.11	.74	1.69	.26	n.s.††
6 - 10	22	8.8	26	9.6	1.06	.57	1.96	.03	n.s.
11 - 15	20	8.0	8	3.0	3.12	1.32	7.35	7.32	< 0.05
16 +	32	12.8	26	9.6	1.54	.96	2.73	2.15	n.s.
Total	250	100.0	271	100.0	1.34†	1.02	1.77	4.22	< 0.05
Unknown:	9		7						

† Mantel - Haenszel estimate.

†† n.s. = not significant at the 5% level.

Mean years employed	10.34 yr	8.65 yr

2063630881

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 59

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY AGE

Number of years employed	Cases No.	Cases %	Compeers No.	Compeers %	ODDS RATIO	95% C.I. Low	95% C.I. High	CHI-SQUARE	p VALUE
30 - 49 years									
Never	11	44.0	15	48.4	1.00				
< 10	8	32.0	16	51.6	.68	.22	2.16	.43	n.s.‡
> 10	6	24.0			17.52	.89	343.56	5.64	< 0.05
Total	25	100.0	31	100.0					
50 - 59 years									
Never	26	28.9	37	41.6	1.00				
< 10	44	48.9	40	44.9	1.57	.81	3.03	1.76	n.s.
> 10	20	22.2	12	13.5	2.37	.99	5.88	3.83	n.s.
Total	90	100.0	89	100.0					
60 -69 years									
Never	47	50.5	54	52.4	1.00				
< 10	23	24.7	33	32.0	.80	.41	1.55	.44	n.s.
> 10	23	24.7	16	15.5	1.65	.78	3.49	1.74	n.s.
Total	93	100.0	103	100.0					
70 or more years									
Never	25	59.5	30	62.5	1.00				
< 10	14	33.3	12	25.0	1.40	.55	3.57	.50	n.s.
> 10	3	7.1	6	12.5	.60	.14	2.65	.46	n.s.
Total	42	100.0	48	100.0					
MANTEL-HAENSZEL:					1.35	.99	1.83	3.64	n.s.

Age calculated by subtracting date of birth from 1 January, 1979.
Unknown duration employed: Cases = 9, Compeers = 7.
n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 60

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY SMOKING STATUS

Number of years employed	Smoked cigarettes: Cases No	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	100	42.0	73	46.2	1.00				
1 - 5	66	27.7	52	32.9	.93	.58	1.49	.10	n.s.††
6 - 10	21	8.8	14	8.9	1.10	.52	2.30	.06	n.s.
11 - 15	19	8.0	6	3.8	2.31	.88	6.07	3.02	n.s.
16 +	32	13.4	13	8.2	1.80	.88	3.66	2.65	n.s.
Total	238	100.0	158	100.0	1.24†	.90	1.71	1.70	n.s.

Number of years employed	Never smoked cigarettes: Cases No	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	9	75.0	62	55.4	1.00				
1 - 5	1	8.3	23	20.5	.30	.04	2.50	1.38	n.s.
6 - 10	1	8.3	12	10.7	.57	.07	4.96	.26	n.s.
11 - 15	1	8.3	2	1.8	3.44	.28	41.97	1.05	n.s.
16 +			13	11.6	.24	.01	4.45	1.06	n.s.
Total	12	100.0	112	100.0	.50†	.17	1.50	1.53	n.s.
OVERALL MANTEL-HAENSZIEL ESTIMATE:					1.14	.84	1.55	.70	n.s.

† Mantel-Haenszel estimate.
†† n.s. - not significant at the 5% level.
Unknown: 9 cases (smoked), 7 compeers (smoked).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 51

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND
CONTROLS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1969

Ever employed	Cases No.	Cases %	Controls No.	Controls %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p value
Yes	141	54.4	135	48.6					
					1.27	.90	1.79	1.81	n.s.
No	118	45.6	143	51.4					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND
CONTROLS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1969 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Controls No.	Controls %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p value
Smokers:									
Yes	134	55.3	97	52.7					
					1.14	.75	1.69	.27	
No	109	44.1	78	47.3					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	3	25.0	48	42.9					
					.44	.11	1.73	1.43	
No	9	75.0	64	57.1					
Total	12	100.0	112	100.0					
Mantel-Haenszel Odds Ratio:					1.04	.72	1.52	.05	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 51 (continued)

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1959

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	128	49.4	116	41.7	1.36	.97	1.92	2.90	n.s.
No	131	50.6	162	58.3					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1959 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smokers:									
Yes	125	50.6	71	43.0	1.36	.91	2.02	2.28	
No	122	49.4	94	57.0					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	3	25.0	45	40.2	.50	.13	1.93	1.05	
No	9	75.0	67	59.8					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.24	.85	1.81	1.25	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 51 (Continued)

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1949

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	99	38.2	91	32.7	1.27	.89	1.81	1.54	n.s.
No	160	61.8	187	67.3					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY PRIOR TO OR DURING 1949 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smokers:									
Yes	97	39.3	56	33.9	1.26	.83	1.90	1.20	
No	150	60.7	109	66.1					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	2	16.7	35	31.3	.44	.09	2.11	2.82	
No	10	83.3	77	68.8					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.16	.78	1.72	.54	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 62

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	79	30.5	70	25.2	1.30	.99	1.90	1.89	n.s.
No	180	69.5	208	74.8					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smokers:									
Yes	79	32.0	42	25.3	1.39	.99	2.15	2.14	n.s.
No	168	68.0	124	74.7					
Total	247	100.0	166	100.0					
Nonsmokers:									
Yes	0		28	25.0	.12	.01	2.07	3.00	n.s.
No	12	100.0	84	75.0					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.21	.79	1.85	.76	n.s.

n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 63

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY AGE

Age Groups (5 Years)†	Employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
30-34 yrs.	Yes					5.00	.04	711.90	.44	n.s.††
	No			2	100.00					
35-39 yrs.	Yes					1.00	.01	73.27	.01	n.s.
	No	2	100.00	2	100.00					
40-44 yrs.	Yes	1	16.67	1	33.33	.40	.02	10.01	.32	n.s.
	No	5	83.33	2	66.67					
45-49 yrs.	Yes	4	23.53	9	36.00	.55	.14	2.19	.74	n.s.
	No	13	76.47	16	64.00					
50-54 yrs.	Yes	14	35.00	8	20.51	2.09	.76	5.75	2.06	n.s.
	No	26	65.00	31	79.49					
55-59 yrs.	Yes	18	34.62	13	25.00	1.59	.68	3.71	1.15	n.s.
	No	34	65.38	39	75.00					
60-64 yrs.	Yes	21	35.00	30	40.00	.81	.37	1.75	.29	n.s.
	No	39	65.00	30	60.00					
65-69 yrs.	Yes	9	23.68	12	21.05	1.16	.44	3.11	.09	n.s.
	No	29	76.32	45	78.95					
70-74 yrs.	Yes	9	28.13	5	18.52	1.72	.50	5.95	.75	n.s.
	No	23	71.88	22	81.48					
75-79+ yrs.	Yes	3	25.00	2	9.52	3.17	.45	22.42	1.42	n.s.
	No	9	75.00	19	90.48					
Total	Yes	79	30.50	70	25.18	1.25	.85	1.83	1.29	n.s.
	No	180	69.50	208	74.82					

†Age calculated by subtracting date of birth from 1 January, 1979.
†† Mantel - Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 54

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY AGE AND SMOKING STATUS

Age groups	Ever employed in a high risk occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked										
30 - 49 yr	Yes	5	20.8	5	23.8	.84	.21	3.44	.06	n.s.
	No	19	79.2	16	76.2					
50 - 59 yr	Yes	32	34.8	12	20.7	2.04	.95	4.40	3.41	n.s.
	No	60	65.2	46	79.3					
60 - 69 yr	Yes	30	33.3	21	30.4	1.14	.58	2.24	.15	n.s.
	No	60	66.7	48	69.6					
70 + yr	Yes	12	29.3	4	22.2	1.45	.40	5.31	.31	n.s.
	No	29	70.7	14	77.8					
Total	Yes	79	32.0	42	25.3	1.40‡	.90	2.19	2.19	n.s.
	No	168	68.0	124	74.7					
Never smoked										
30 - 49 yr	Yes			5	45.5	.39	.01	11.76	.30	n.s.
	No	1	100.0	6	54.5					
50 - 59 yr	Yes			9	27.3	2.58	.05	139.54	.22	n.s.
	No			24	72.7					
60 - 69 yr	Yes			11	28.9	.14	.01	2.65	2.22	n.s.
	No	8	100.0	27	71.1					
70 + yr	Yes			3	10.0	1.12	.05	26.59	.01	n.s.
	No	3	100.0	27	90.0					
Total	Yes	0		28	25.0	.41‡	.09	1.80	1.41	n.s.
	No	12	100.0	84	75.0					
OVERALL MANTEL-HAENSZEL ESTIMATE:						1.24	.82	1.90	1.02	n.s.

Mantel-Haenszel estimate.

‡‡ n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 65

FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND CONTROLS IN A HIGH RISK OCCUPATION

Frequency of employment	Cases No.	%	Controls No.	%
1	42	53.2	38	42.9
2	17	21.5	22	31.4
3	9	11.4	6	8.6
4	1	1.3	7	10.0
5 +	8	10.1	5	7.1
Total	79	100.0	78	100.0
Mean:	2.11		2.13	
Standard deviation:	1.3		2.04	

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APPENDIX C TABLE 66

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION

Frequency of employment	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	180	69.5	208	74.8	1.00				
1	42	16.2	30	10.8	1.62	.97	2.69	3.47	n.s.‡
2	17	6.6	22	7.9	.89	.46	1.73	.11	n.s.
3	9	3.5	6	2.2	1.73	.61	4.96	1.07	n.s.
4	3	1.2	7	2.5	.50	.13	1.94	1.05	n.s.
5 +	8	3.1	5	1.8	1.85	.59	5.75	1.16	n.s.
Total	259	100.0	278	100.0	1.29‡‡	.92	1.82	2.19	n.s.
Mean times employed:	2.11		2.19						
Standard deviation:	1.3		2.04						

APPENDIX C TABLE 67

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY SMOKING STATUS

Frequency of employment	Smoked cigarettes: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	168	68.0	124	74.7	1.00				
1	42	17.0	13	7.8	2.38	1.23	4.63	6.87	< 0.05
2 - 11	37	15.0	29	17.5	.94	.55	1.61	.05	n.s.
Total	247	100.0	166	100.0	1.40‡‡	.93	2.10	2.58	n.s.
Never smoked cigarettes									
Never	12	100.0	94	75.0	1.00				
1			17	15.2	.19	.01	3.42	1.55	n.s.
2 - 11			11	9.8	.29	.02	5.30	.77	n.s.
Total	12	100.0	112	100.0	.23‡‡	.04	1.54	2.22	n.s.
Overall Mantel-Haenszel estimate:					1.24	.83	1.83	1.10	n.s.

‡ n.s. = not significant at the 5% level.
‡‡ Mantel-Haenszel estimate.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 68

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY AGE

Number of times employed	Case No.	Case %	Compeer No.	Compeer %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
40 - 49 years									
Never	18	78.3	18	64.3	1.00				
1	4	17.4	2	7.1	2.00	.32	12.33	.57	n.s.
2-11	1	4.3	8	28.6	.13	.01	1.10	4.47	< 0.05
Total	23	100.0	28	100.0	.52	.16	1.66	1.21	n.s.
50 - 59 years									
Never	60	65.9	70	76.9	1.00				
1	16	17.6	8	8.8	2.33	.93	5.83	3.41	n.s.
2-11	15	16.5	13	14.3	1.35	.59	3.06	.51	n.s.
Total	91	100.0	91	100.0	1.73	.95	3.16	3.16	n.s.
60 - 69 years									
Never	68	68.7	75	70.1	1.00				
1	15	15.2	19	17.8	.87	.41	1.85	.12	n.s.
2-11	16	16.2	13	12.1	1.36	.61	3.03	.55	n.s.
Total	99	100.0	107	100.0	1.07	.62	1.85	.06	n.s.
70 or more years									
Never	32	72.7	41	85.4	1.00				
1	7	15.9	1	2.1	8.97	1.05	76.67	5.51	< 0.05
2-11	5	11.4	6	12.5	1.07	.30	3.82	.01	n.s.
Total	44	100.0	48	100.0	2.23	.84	5.93	2.59	n.s.
OVERALL MANTEL-HAENSZEL:					1.30	.91	1.85	2.12	n.s.

Never employed 30 to 39 years of age: Cases = 2; Compeers = 4.

* Age calculated by subtracting date of birth from 1 January, 1979.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

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APPENDIX C TABLE 70

ODDS RATIO FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION

Number of years employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	190	71.1	208	76.8	1.00				
1 - 3	29	11.5	18	6.6	1.86	1.00	3.46	3.94	< 0.05
4 - 6	12	4.7	18	6.6	.77	.36	1.64	.46	n.s.††
7 - 9	5	2.0	8	3.0	.72	.23	2.25	.32	n.s.
10 +	27	10.7	19	7.0	1.64	.88	3.05	2.50	n.s.
Total	253	100.0	271	100.0	1.33†	.93	1.89	2.45	n.s.

Unknown: 6 7

Mean years employed: 9.89 yr 8.73 yr

APPENDIX C TABLE 71

ODDS RATIO FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY SMOKING STATUS

Number of years employed	Smoked cigarettes: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	168	69.7	124	77.5	1.00				
1 - 3	29	12.0	9	5.6	2.38	1.09	5.20	4.93	< 0.05
4 - 6	12	5.0	12	7.5	.74	.32	1.70	.51	n.s.††
7 - 9	5	2.1	3	1.9	1.23	.29	5.24	.08	n.s.
10 +	27	11.2	12	7.5	1.66	.81	3.41	1.94	n.s.
Total	241	100.0	160	100.0	1.48†	.98	2.25	3.44	n.s.

Number of years employed	Never smoked cigarettes: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	12	100.0	84	75.7					
					.12	.01	2.14	2.87	n.s.
1 or more	0		27	24.3					
Total	12	100.0	111	100.0					

MANTEL-HAENSZEL ESTIMATE: 1.31 .87 1.96 1.71 n.s.

Unknown: 6 cases (smoked), 6 compeers (smoked), 1 compeer (never smoked).

†Mantel-Haenszel estimate.

†† n.s. = not significant at the 5% level

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 72

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY AGE

Number of years employed	Case No.	Case %	Compeer No.	Compeer %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
30 - 49 years									
Never	20	80.0	22	71.0	1.00				
1 - 3	1	4.0	3	9.7	.37	.04	3.82	.75	n.s.‡
4 +	4	16.0	6	19.4	.73	.18	2.98	.19	n.s.
Total	25	100.0	31	100.0					
50 - 59 years									
Never	60	65.9	70	77.8	1.00				
1 - 3	15	16.5	6	6.7	2.92	1.06	7.99	4.62	< 0.05
4 +	16	17.6	14	15.6	1.33	.60	3.00	.50	n.s.
Total	91	100.0	90	100.0					
60 - 69 years									
Never	68	72.3	75	73.5	1.00				
1 - 3	6	6.4	7	6.9	.95	.30	2.95	.01	n.s.
4 +	20	21.3	20	19.6	1.10	.55	2.22	.08	n.s.
Total	94	100.0	102	100.0					
70 or more years									
Never	32	74.4	41	85.4	1.00				
1 - 3	7	16.3	2	4.2	4.48	.97	23.07	3.70	n.s.
4 +	4	9.3	5	10.4	1.03	.25	4.13	.01	n.s.
Total	43	100.0	48	100.0					
MANTEL-HAENSZEL:					1.34	.92	1.93	2.39	n.s.

Unknown: 6 7

Never employed 30 to 39 years of age: Cases = 2; Compeers = 4.

Age calculated by subtracting date of birth from 1 January, 1979.

‡ n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 73

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1969

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Yes	72	27.8	65	23.4	1.28	.86	1.86	1.15	n.s.
No	187	72.2	213	76.6					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1969 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Smokers:									
Yes	72	29.1	40	24.2	1.29	.82	2.02	1.20	n.s.
No	175	70.9	125	75.8					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	0	.0	25	22.3	.14	.01	2.40	2.49	n.s.
No	12	100.0	87	77.7					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.14	.77	1.76	.33	n.s.

2063630896

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 73 (continued)

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1959

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Yes	59	22.8	54	19.4	1.22	.81	1.85	.72	n.s.
No	200	77.2	224	80.6					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1959 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Smokers:									
Yes	59	23.9	33	20.0	1.26	.78	2.03	.86	n.s.
No	188	76.1	132	80.0					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	0	.0	21	18.8	.17	.01	2.99	1.86	n.s.
No	12	100.0	91	81.3					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.12	.70	1.79	.23	n.s.

2063630897

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 72 (continued)

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1949

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Yes	50	19.3	36	12.9	1.61	1.01	2.56	3.57	n.s.
No	209	80.7	242	87.1					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION PRIOR TO OR DURING 1949 BY SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	Low	High	Chi-Square	p Value
Smokers:									
Yes	50	20.2	27	16.4	1.30	.77	2.17	.98	n.s.
No	197	79.8	138	83.6					
Total	247	100.0	165	100.0					
Nonsmokers:									
Yes	0	.0	9	8.0	.44	.02	7.95	.33	n.s.
No	12	100.0	103	92.0					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.24	.75	2.06	.69	n.s.

2063630898

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 74

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS
IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION

Employed in both industry and occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	65	25.1	51	18.3	1.49	.99	2.26	3.61	>.05
No	194	74.9	227	81.7					
Total	259	100.0	278	100.0					

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS
IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION BY SMOKING STATUS

Employed in both industry and occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	65	26.3	32	19.3	1.50	.92	2.41	2.74	n.s.
No	182	73.7	134	80.7					
Total	247	100.0	166	100.0					
Never smoked cigarettes									
Yes			19	17.0	.19	.01	3.38	1.57	n.s.
No	12	100.0	93	83.0					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.34	.84	2.13	1.51	n.s.

n.s. = not significant at the 5% level.

2063630899

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 75

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATOIN BY AGE

Age groups (5 years)‡	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
30-34 yrs.			2	100.00	5.00	.04	711.87	.44	n.s.‡‡
35-39 yrs.	2	100.00	2	100.00	1.00	.01	73.27	.01	n.s.
40-44 yrs.	1	16.67	1	33.33	.40	.02	10.02	.32	n.s.
	5	83.33	2	66.67					
45-49 yrs.	4	23.53	4	16.00	1.62	.34	7.60	.37	n.s.
	13	76.47	21	84.00					
50-54 yrs.	13	32.50	6	15.38	2.65	.89	7.90	3.17	n.s.
	27	67.50	33	84.62					
55-59 yrs.	16	30.77	9	17.31	2.12	.84	5.38	2.58	n.s.
	36	69.23	43	82.69					
60-64 yrs.	15	25.00	14	28.00	.86	.37	2.01	.13	n.s.
	45	75.00	36	72.00					
65-69 yrs.	6	15.79	11	19.30	.78	.26	2.34	.19	n.s.
	32	84.21	46	80.70					
70-74 yrs.	7	21.88	4	14.81	1.61	.42	6.23	.48	n.s.
	25	78.13	23	85.19					
75-79+ yrs.	3	25.00	2	9.52	3.17	.45	22.42	1.42	n.s.
	9	75.00	19	90.48					
MANTEL-HAENSZEL:	65	25.10	51	18.35	1.43	.95	2.16	2.91	n.s.
	194	74.90	227	81.65					

‡Age calculated by subtracting date of birth from 1 January, 1979.
‡‡ n.s. = not significant at the 5% level.

2063630900

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 76

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS
IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION BY AGE AND SMOKING STATUS

Age groups‡	Ever employed in a high risk occupation and industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked										
30 - 49 yr	Yes	5	20.8	2	9.5	2.50	.43	14.51	1.09	n.s.
	No	19	79.2	19	90.5					
50 - 59 yr	Yes	29	31.5	9	15.5	2.51	1.09	5.78	4.82	< 0.05
	No	63	68.5	49	84.5					
60 - 69 yr	Yes	21	23.3	17	24.6	.93	.45	1.94	.04	n.s.
	No	69	76.7	52	75.4					
70 + yr	Yes	10	24.4	4	22.2	1.13	.30	4.23	.03	n.s.
	No	31	75.6	14	77.8					
Total	Yes	65	26.3	32	19.2	1.48‡	.92	2.38	2.55	n.s.
	No	182	73.7	134	80.7					
Never smoked										
30 - 49 yr	Yes			3	27.3	.81	.03	25.10	.01	n.s.
	No	1	100.0	8	72.7					
50 - 59 yr	Yes			6	18.2	4.23	.08	233.81	.58	n.s.
	No			27	81.8					
60 - 69 yr	Yes			8	21.1	.21	.01	4.04	1.27	n.s.
	No	8	100.0	30	78.9					
70 + yr	Yes			2	6.7	1.63	.06	41.29	.09	n.s.
	No	2	100.0	28	93.3					
Total	Yes	0		19	17.0	.64‡	.14	3.00	.33	n.s.
	No	12	100.0	93	83.0					
OVERALL MANTEL-HAENSZEL ESTIMATE:						1.36	.86	2.15	1.78	n.s.

Mantel-Haenszel estimate.
‡‡ n.s. = not significant at the 5% level.

2063630901

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 77

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION BY PACK-YEARS OF CIGARETTES SMOKED

Age groups‡	Pack-years smoked	Ever employed	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	α Value
30 - 54 yr.	1 - 34.21	Yes	7	15.79	5	11.54	1.44	.26	8.05	.17	n.s.‡
		No	16	84.21	23	88.46					
	34.22 - 65.70	Yes	11	44.00	2	13.33	5.12	.95	27.55	3.74	n.s.
		No	14	56.00	13	86.67					
	65.71 +	Yes	3	18.75	1	16.67	1.15	.10	13.88	.01	n.s.
		No	13	81.25	5	83.33					
55 - 64 yr.	1 - 34.21	Yes	6	26.09	4	23.53	1.15	.28	4.92	.03	n.s.
		No	17	73.91	13	76.47					
	34.22 - 65.70	Yes	10	23.81	7	25.93	.89	.29	2.73	.04	n.s.
		No	32	76.19	20	74.07					
	65.71 +	Yes	15	36.59	5	27.78	1.50	.45	5.04	.43	n.s.
		No	26	63.41	13	72.22					
65 + yr.	1 - 34.21	Yes	1	10.00	3	15.00	.63	.06	6.96	.14	n.s.
		No	9	90.00	17	85.00					
	34.22 - 65.70	Yes	6	26.09	5	22.73	1.20	.31	4.69	.07	n.s.
		No	17	73.91	17	77.27					
	65.71 +	Yes	6	17.65	0	.00	3.42	.17	67.82	.72	n.s.
		No	28	82.35	7	100.00					
Overall Mantel-Haenszel		Yes	61	26.29	31	19.18	1.42	.85	2.37	1.77	n.s.
		No	172	57.31	128	80.82					
Never smoked:			12		112						
Unknown duration smoked:			14		7						
Total:			259		278						

‡ Age estimated by subtracting date of birth from 1 January, 1979.
‡‡n.s. = Not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 3

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION BY VITAL STATUS

Living

Ever employed	Cases No.	Cases %	Compeers No	Compeers %	Odds Ratio	95%C.I. Low	95%C.I. High	Chi-Square	p Value
Yes	30	68.2	52	66.7	1.07	.49	2.36	.02	n.s.
No	14	31.8	26	33.3					
Total	44	100.0	78	100.0					

Deceased

Ever employed	Cases No.	Cases %	Compeers No	Compeers %	Odds Ratio	95%C.I. Low	95%C.I. High	Chi-Square	p Value
Yes	135	62.8	109	54.5	1.41	.95	2.09	2.94	n.s.
No	80	37.2	91	45.5					
Total	215	100.0	200	100.0	1.33	.94	1.9	2.59	n.s.

2063630903

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 79

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN EITHER A HIGH RISK INDUSTRY OR A HIGH RISK OCCUPATION BY VITAL STATUS AND SMOKING STATUS

Ever employed	Cases No.	Cases %	Compeers No	Compeers %	Odds Ratio	95%C.I. Low	95%C.I. High	Chi-Square	p Value
Living, smoked cigarettes									
Yes	30	71.4	29	69.0					
					1.12	.44	2.86	.06	n.s.††
No	12	28.6	13	31.0					
Total	42	100.0	42	100.0					
Living, never smoked cigarettes									
Yes			23	63.9					
					.11	.01	2.57	2.54	n.s.
No	2	100.0	13	36.1					
Total	2	100.0	36	100.0					
Mantel-Haenszel among the living:					.86	.27	2.01	.12	n.s.
Deceased, smoked cigarettes									
Yes	131	63.9	73	58.9					
					1.24	.78	1.95	.81	n.s.
No	74	36.1	51	41.1					
Total	205	100.0	124	100.0					
Deceased, never smoked cigarettes									
Yes	3	30.0	36	47.4					
					.48	.11	1.98	1.08	n.s.
No	7	70.0	40	52.6					
Total	10	100.0	76	100.0					
Mantel-Haenszel among the deceased:					1.12	.72	1.73	.27	n.s.
OVERALL MANTEL-HAENSZEL:					1.06	.72	1.56	.09	n.s.

† Mantel-Haenszel odds ratio.
†† n.s. = not significant at the 5% level

2063630904

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 20

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY VITAL STATUS

Ever employed	Cases No	Cases %	Compeers No.	Compeers %	ODDS RATIO	95% C.I. Low	95% C.I. High	CHI-SQUARE	p VALUE
Living									
Yes	27	61.4	45	57.7	1.16	.55	2.48	.16	n.s.
No	17	38.6	33	42.3					
Total	44	100.0	78	100.0					
Deceased									
Yes	123	57.2	97	48.5	1.42	.96	2.09	3.15	n.s.
No	92	42.8	103	51.5					
Total	215	100.0	200	100.0					
Overall Mantel-Haenszel estimate:					1.36	.97	1.92	3.09	n.s.

2063630905

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 31

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY VITAL STATUS

Number of times employed	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	17	38.6	33	42.3	1.00				
1	9	20.5	13	16.7	1.34	.48	3.77	.22	n.s.††
2	9	20.5	10	12.8	1.75	.60	5.11	1.05	n.s.
3	4	9.1	11	14.1	.71	.20	2.55	.29	n.s.
4	1	2.3	6	7.7	.22	.04	2.91	1.10	n.s.
5	4	9.1	7	7.8	2.59	.62	12.91	1.41	n.s.
6			2	2.6	.38	.02	8.42	.40	n.s.
Total	44	100.0	78	100.0	1.15†	.66	1.99	.24	n.s.

Number of times employed	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	92	42.8	103	51.5	1.00				
1	49	22.8	54	27.0	1.02	.63	1.64	.01	n.s.
2	36	16.7	22	11.0	1.93	1.01	3.74	3.96	< 0.05
3	16	7.4	11	5.5	1.63	.72	3.69	1.39	n.s.
4	10	4.7	6	3.0	1.97	.65	5.93	1.39	n.s.
5	5	2.3	2	1.0	2.80	.53	14.78	1.59	n.s.
6	6	2.8			14.55	.81	261.76	5.64	< 0.05
7	1	.5	2	1.0	.56	.05	6.28	.22	n.s.
Total	215	100.0	200	100.0	1.48†	1.09	2.01	6.40	< 0.05

Overall Mantel-Haenszel estimate: 1.40 1.07 1.82 6.00 < 0.05

† Mantel-Haenszel estimate.

†† n.s. = not significant at the 5% level

	Living	Deceased
Mean frequency employed:		
Living:	2.0	2.5
Standard deviation:	1.4	1.6
Deceased:	2.3	1.9
Standard deviation:	1.5	1.3

2063630906

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 32

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY VITAL STATUS AND SMOKING STATUS

Frequency of employment in a risk industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Living, smoked cigarettes									
Never employed	15	35.7	16	38.1	1.00				
1	9	21.4	8	19.0	1.20	.37	3.92	.09	n.s.††
2	9	21.4	6	14.3	1.80	.46	6.59	.55	n.s.
3	4	9.5	5	11.9	.85	.19	3.79	.04	n.s.
4 or more	5	11.9	7	16.7	.76	.20	2.93	.16	n.s.
Total	42	100.0	42	100.0	1.09†	.57	2.10	.07	n.s.
Living, never smoked cigarettes									
Never employed	2	100.0	17	47.2	1.00				
Once or more			19	52.8	.18	.01	4.00	1.44	n.s.
Total	2	100.0	36	100.0					
Mantel-Haenszel among the living:					.98	.52	1.84	.01	n.s.
Deceased, smoked cigarettes									
Never employed	85	41.5	58	46.8	1.00				
1	48	23.4	40	32.3	.82	.48	1.40	.53	n.s.
2	35	17.1	13	10.5	1.84	.90	3.77	2.79	n.s.
3	15	7.3	7	5.6	1.46	.56	3.81	.51	n.s.
4 or more	22	10.7	6	4.8	2.50	.96	6.55	3.66	n.s.
Total	205	100.0	124	100.0	1.31†	.92	1.87	2.17	n.s.
Deceased, never smoked cigarettes									
Never employed	7	70.0	45	59.2	1.00				
Once or more	3	30.0	31	40.8	.62	.15	2.59	.47	n.s.
Total	10	100.0	76	100.0					
Mantel-Haenszel among the deceased:					1.25	.98	1.76	1.80	n.s.
OVERALL MANTEL-HAENSZEL ESTIMATE:					1.18	.87	1.60	1.17	n.s.

†† n.s. = not significant at the 5% level.

2063630907

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 83

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY VITAL STATUS

Number of years employed	Living Cases No	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	17	38.6	33	42.9	1.00				
1 - 5	14	31.8	19	24.7	1.43	.58	3.54	.60	n.s.**
6 - 10	5	11.4	9	11.7	1.08	.31	3.73	.01	n.s.
11 - 15	2	4.5	1	1.3	3.88	.33	45.94	1.31	n.s.
16 +	6	13.6	15	19.5	.78	.26	2.36	.20	n.s.
Total	44	100.0	77	100.0	1.19*	.66	2.15	.35	n.s.

Number of years employed	Deceased Cases No	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	92	44.7	103	53.1	1.00				
1 - 5	53	25.7	56	28.9	1.06	.66	1.69	.06	n.s.
6 - 10	17	8.3	17	8.8	1.12	.54	2.32	.09	n.s.
11 - 15	18	8.7	7	3.6	2.88	1.15	7.20	5.46	< 0.05
16 +	26	12.6	11	5.7	2.65	1.24	5.65	6.63	< 0.05
Total	206	100.0	194	100.0	1.47*	1.07	2.02	5.52	< 0.05

OVERALL MANTEL-HAENSZEL ESTIMATE: 1.40 1.06 1.85 5.52 < 0.05

* Mantel-Haenszel estimate.

** n.s. - not significant at the 5% level.

Unknown: 9 deceased cases,
6 deceased compeers, 1 living compeer.

2066360908

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 84

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK INDUSTRY BY VITAL STATUS AND SMOKING STATUS

Number of years employed	Living, smoked cigarettes: Cases No	Cases %	Compeers# No.	Compeers# %	Odds Ratio	95% Confidence interval Low	High	Chi-Square	p Value
Never	15	35.7	16	39.0	1.00				
1 - 5	14	33.3	12	29.3	1.24	.44	3.54	.17	n.s.##
6 - 10	5	11.9	4	9.8	1.33	.30	5.93	.14	n.s.
11 - 15	2	4.8	1	2.4	2.13	.17	26.03	.37	n.s.
16 +	6	14.3	8	19.5	.80	.22	2.86	.19	n.s.
Total	42	100.0	41	100.0	1.16#	.58	2.30	.18	n.s.
Living, never smoked cigarettes									
Never	2	100.0	17	47.2	1.00				
1 or more			19	52.8	.18	.01	4.00	1.44	n.s.
Total	2	100.0	36	100.0					
Mantel-Haenszel among the living:					1.03	.53	1.98	.01	n.s.
Deceased, smoked cigarettes									
Never	85	43.4	58	49.2	1.00				
1 - 5	52	26.5	40	33.9	.89	.52	1.51	.20	n.s.
6 - 10	16	8.2	10	8.5	1.09	.46	2.57	.04	n.s.
11 - 15	17	8.7	5	4.2	2.32	.81	6.64	2.57	n.s.
16 +	26	13.3	5	4.2	3.55	1.29	9.78	6.58	< 0.05
Total	196	100.0	118	100.0	1.34#	.93	1.95	2.43	n.s.
Deceased, never smoked cigarettes									
Never	7	70.0	45	59.2	1.00				
1 - 5	1	10.0	16	21.1	.40	.05	3.52	.72	n.s.
6 - 10	1	10.0	7	9.2	.92	.10	8.64	.01	n.s.
11 - 15	1	10.0	2	2.6	3.21	.26	40.32	.90	n.s.
16 +			6	7.9	.47	.02	9.17	.26	n.s.
Total	10	100.0	76	100.0	.74#	.23	2.37	.25	n.s.
Mantel-Haenszel among the deceased:					1.27	.89	1.81	1.74	n.s.
OVERALL MANTEL-HAENSZEL ESTIMATE:					1.21	.89	1.65	1.44	n.s.

n.s. - not significant at the 5% level.
Unknown: 9 deceased cases (smokers),
6 deceased compeers and 1 living compeer (smokers).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 85

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY VITAL STATUS

Ever employed	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	15	34.1	23	29.5	1.24	.56	2.73	.28	n.s.*
No	29	65.9	55	70.5					
Total	44	100.0	78	100.0					
Ever employed	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	64	29.8	47	23.5	1.38	.89	2.14	2.08	n.s.
No	151	70.2	153	76.5					
Total	215	100.0	200	100.0					
Overall Mantel-Haenszel estimate:					1.35	.92	1.97	2.30	n.s.

* n.s. = not significant at the 5% level.

2063630910

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 86

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY VITAL STATUS

Number of times employed	Living Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never	29	65.9	55	70.5	1.00				
1	8	18.2	10	12.8	1.52	.54	4.26	.63	n.s.‡
2 - 11	7	15.9	13	16.7	1.02	.37	2.84	.01	n.s.
Total	44	100.0	78	100.0	1.24‡	.60	2.56	.33	n.s.
Number of times employed	Deceased Cases No.	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never	151	70.2	153	76.5	1.00				
1	34	15.8	20	10.0	1.72	.95	3.13	3.24	n.s.
2 - 11	30	14.0	27	13.5	1.13	.64	1.98	.17	n.s.
Total	215	100.0	200	100.0	1.38‡	.92	2.08	2.40	n.s.
Overall Mantel-Haenszel estimate:					1.35	.94	1.92	2.68	n.s.

‡ Mantel-Haenszel estimate.

2063630911

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 87

ODDS RATIOS FOR FREQUENCY OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN A HIGH RISK OCCUPATION BY VITAL STATUS AND SMOKING STATUS

Frequency employed	Living, smoked cigarettes Cases No	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never	27	64.3	31	73.8	1.00				
Once	8	19.0	2	4.8	4.59	.90	23.51	3.82	n.s.
> Once	7	16.7	9	21.4	.89	.29	2.72	.04	n.s.
Total	42	100.0	42	100.0	1.61‡	.68	3.83	1.18	n.s.
	Living, never smoked cigarettes								
Never	2	100.0	24	66.7	1.00				
1 or more			12	33.3	.39	.02	8.81	.37	n.s.
Total	2	100.0	36	100.0					
Mantel-Haenszel among the living:					1.42	.62	3.22	.69	n.s.
	Deceased, smoked cigarettes								
Frequency employed	Cases No	%	Compeers No.	%	Odds Ratio	95% C.I. Low	High	Chi-Square	p Value
Never	141	68.8	93	75.0	1.00				
Once	34	16.6	11	8.9	1.84	.98	4.22	3.78	n.s.
> Once	30	14.6	20	16.1	.99	.53	1.85	.01	n.s.
Total	205	100.0	124	100.0	1.37‡	.86	2.18	1.71	n.s.
	Deceased, never smoked cigarettes								
Never	10	100.0	60	78.9	1.00				
1 or more			16	21.1	.17	.01	3.14	1.76	n.s.
Total	10	100.0	76	100.0					
Mantel-Haenszel among the deceased:					1.22	.78	1.94	.81	n.s.
OVERALL MANTEL-HAENSZEL ESTIMATE:					1.27	.85	1.89	1.41	n.s.

‡ Mantel-Haenszel estimate.
‡‡ n.s. - not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 88

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS WERE EMPLOYED IN A HIGH RISK OCCUPATION BY VITAL STATUS

Number of years employed	Living Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	29	65.9	55	70.5	1.00				
1 - 3 yr	5	11.4	6	7.7	1.58	.44	5.62	.51	n.s.††
4 - 6 yr	4	9.1	6	7.7	1.26	.33	4.84	.12	n.s.
7 - 9 yr	1	2.3	2	2.6	.95	.08	10.90	.01	n.s.
10 - 40 yr	5	11.4	9	11.5	1.05	.32	3.43	.01	n.s.
Total	44	100.0	78	100.0	1.24†	.62	2.48	.36	n.s.

Number of years employed	Deceased Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	151	72.2	153	79.3	1.00				
1 - 3 yr	24	11.5	12	6.2	2.03	.98	4.20	3.72	n.s.
4 - 6 yr	8	3.8	12	6.2	.68	.27	1.70	.70	n.s.
7 - 9 yr	4	1.9	6	3.1	.68	.19	2.44	.36	n.s.
10 - 40 yr	22	10.5	10	5.2	2.23	1.02	4.87	4.22	< 0.05
Total	209	100.0	193	100.0	1.45†	.95	2.21	3.03	n.s.
OVERALL MANTEL-HAENSZEL:					1.39	.97	1.99	3.25	n.s.

† Mantel-Haenszel estimate.
†† n.s. = not significant at the 5% level.
Unknown: 6 deceased cases, 7 deceased compeers.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 89

ODDS RATIOS FOR DURATION OF EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS WERE EMPLOYED IN A HIGH RISK OCCUPATION BY VITAL STATUS AND SMOKING STATUS

Number of years employed	Living, smoked cigarettes: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	27	64.3	31	73.8	1.00				
1 - 3 yr	5	11.9	3	7.1	1.91	.42	8.76	.72	n.s.
4 - 6 yr	4	9.5	2	4.8	2.30	.39	13.54	.88	n.s.
7 - 9 yr	1	2.4	1	2.4	1.15	.07	19.25	.01	n.s.
10 - 40 yr	5	11.9	5	11.9	1.15	.30	4.40	.04	n.s.
Total	42	100.0	42	100.0	1.57‡	.69	3.60	1.14	n.s.
	Living, never smoked cigarettes								
Never	2	100.0	24	66.7	1.00				
1 or more			12	33.3	.39	.02	8.81	.37	n.s.
Total	2	100.0	36	100.0					
Mantel-Haenszel among living:					1.40	.63	3.08	.39	n.s.
Number of years employed	Deceased, smoked cigarettes: Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Never	141	70.9	93	78.9	1.00				
1 - 3 yr	24	12.1	6	5.1	2.64	1.04	6.70	4.42	< 0.05
4 - 6 yr	8	4.0	10	8.5	.53	.20	1.39	1.73	n.s.
7 - 9 yr	4	2.0	2	1.7	1.32	.24	7.35	.10	n.s.
10 - 40 yr	22	11.1	7	5.9	2.07	.85	5.05	2.67	n.s.
Total	199	100.0	118	100.0	1.51‡	.93	2.46	2.76	n.s.
	Deceased, never smoked cigarettes								
Never	10	100.0	60	80.0	1.00				
1 or more			15	20.0	.19	.01	3.35	1.61	n.s.
Total	10	100.0	75	100.0					n.s.
Mantel-Haenszel among deceased:					1.35	.84	2.17	1.56	n.s.
OVERALL MANTEL-HAENSZEL ESTIMATE:					1.36	.91	2.05	2.24	n.s.

‡ Mantel-Haenszel estimate.
‡‡ n.s. = not significant at the 5% level.
Unknown: 6 deceased cases (smoked),
6 deceased compeers (smoked), 1 living compeer (never smoked)

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 90

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS
IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION BY VITAL STATUS

Employed in both industry and occupation	Cases No.	Cases %	Compeers No.	Compeers %	ODDS RATIO	95% C.I. Low	95% C.I. High	CHI-SQUARE	p VALUE
Living									
Yes	12	27.3	16	20.5	1.45	.61	3.44	.73	n.s.
No	32	72.7	62	79.5					
Total	44	100.0	78	100.0					
Deceased									
Yes	53	24.7	35	17.5	1.54	.96	2.49	3.17	n.s.
No	162	75.3	165	82.5					
Total	215	100.0	200	100.0					
Mantel-Haenszel estimate:					1.52	1.00	2.31	3.88	< 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 91

ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN BOTH A HIGH RISK INDUSTRY AND A HIGH RISK OCCUPATION BY VITAL STATUS AND SMOKING STATUS

Employed in both industry and occupation	Living, smoked cigarettes Cases No.	%	Compeers No	%	Odds Ratio	95%C.I. Low	High	Chi-Square	p Value
Yes	12	28.6	8	19.0	1.70	.61	4.72	1.05	n.s.*
No	30	71.4	34	81.0					
Total	42	100.0	42	100.0					
	Living, never smoked cigarettes								
Yes			8	22.2	.67	.03	15.76	.06	n.s.
No	2	100.0	28	77.8					
Total	2	100.0	36	100.0					
Mantel-Haenszel among the living:					1.54	.59	4.04	.77	n.s.
Employed in both industry and occupation	Deceased, smoked cigarettes Cases No.	%	Compeers No	%	Odds Ratio	95%C.I. Low	High	Chi-Square	p Value
Yes	53	25.9	24	19.4	1.45	.84	2.50	1.82	n.s.
No	152	74.1	100	80.6					
Total	205	100.0	124	100.0					
	Deceased, never smoked cigarettes								
Yes			11	14.5	.27	.01	5.00	.89	n.s.
No	10	100.0	65	85.5					
Total	10	100.0	76	100.0					
Mantel-Haenszel among the deceased:					1.32	.79	2.24	1.08	n.s.
OVERALL MANTEL-HAENSZEL:					1.37	.86	2.18	1.76	n.s.

* n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 92

ODDS RATIOS FOR FAMILY HISTORY OF LUNG CANCER AMONG FEMALE LUNG CANCER CASES AND COMPEERS

Family history of lung cancer	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	39	15.9	18	6.9	2.56	1.42	4.60	9.41	< 0.05
No	206	84.1	243	93.1					
Total	245	100.0	261	100.0					
Unknown:	14		17						

ODDS RATIOS FOR FAMILY HISTORY OF LUNG CANCER AMONG FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

	Smoked cigarettes								
Family history of lung cancer	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	38	16.2	11	7.3	2.47	1.22	5.00	6.63	< 0.05
No	196	82.8	140	92.7					
Total	234	100.0	151	100.0					
	Never smoked cigarettes								
Yes	1	9.1	7	6.4	1.46	.16	13.07	.09	n.s.
No	10	90.9	102	93.6					
Total	11	100.0	109	100.0					
Mantel-Haenszel odds ratio:					2.37	1.27	4.59	6.64	< 0.05
Unknown:									
Smokers	13		14						
Nonsmokers	1		3						

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 93

ODDS RATIO FOR ALCOHOL CONSUMPTION BY FEMALE LUNG CANCER CASES AND COMPEERS

Drank alcohol	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	208	81.9	189	68.0					
					2.13	1.41	3.20	13.55	< 0.05
No	46	18.1	89	32.0					
Total	254	100.0	278	100.0					

ODDS RATIO FOR ALCOHOL CONSUMPTION BY FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

	Cases		Compeers		Odds	95% C.I.		Chi-	p
Drank alcohol	No.	%	No.	%	Ratio	Low	High	Square	Value
Smoked cigarettes									
Yes	201	83.1	139	83.7					
					.95	.56	1.62	.03	n.s.
No	41	16.9	27	16.3					
Total	242	100.0	166	100.0					
Never smoked cigarettes									
Yes	7	58.3	50	44.6					
					1.74	.52	5.80	.82	n.s.
No	5	41.7	62	55.4					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					1.05	.85	1.71	.04	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 94

ODDS RATIO FOR USE OF HAIR SPRAY BY FEMALE LUNG CANCER CASES AND COMPEERS

Used hair spray	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	200	80.3	216	80.3	1.00	.65	1.54	.01	n.s.
No	49	19.7	53	19.7					
Total	249	100.0	269	100.0					

ODDS RATIO FOR USE OF HAIR SPRAY BY FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

Used hair spray	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	191	80.3	135	83.3	.81	.48	1.37	.61	n.s.
No	47	19.7	27	16.7					
Total	238	100.0	162	100.0					
Never smoked cigarettes									
Yes	9	81.8	80	74.8	1.52	.31	7.47	.27	n.s.
No	2	18.2	27	25.2					
Total	11	100.0	107	100.0					
Mantel-Haenszel odds ratio:					.87	.63	1.42	.31	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 95

ODDS RATIO FOR USE OF HAND-HELD HAIR DRYER BY FEMALE LUNG CANCER CASES AND COMPEERS

Used hair dryer	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	61	24.0	55	20.0	1.26	.84	1.91	1.21	n.s.
No	193	76.0	220	80.0					
Total	254	100.0	275	100.0					

ODDS RATIO FOR USE OF HAND-HELD HAIR DRYER BY FEMALE LUNG CANCER CASES AND COMPEERS BY SMOKING STATUS

Used hair dryer	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	58	23.9	35	21.2	1.16	.72	1.87	.39	n.s.
No	185	76.1	130	78.8					
Total	243	100.0	165	100.0					
Never smoked cigarettes									
Yes	3	27.3	20	18.2	1.69	.41	6.93	.54	n.s.
No	8	72.7	90	81.8					
Total	11	100.0	110	100.0					
Mantel-Haenszel odds ratio:					1.20	.77	1.89	.66	n.s.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 96

USUAL OCCUPATION OF HUSBAND OF LUNG CANCER CASES AND COMPEERS.

CATEGORIES OF OCCUPATIONS	Cases No.	Cases %	Compeers No.	Compeers %
Professional, Technical, and Managerial (001-199)	87	33.5	82	30.7
Clerical and Sales (201-299)	36	14.5	37	13.9
Service (301-389)	6	2.4	13	4.9
Agricultural, Fishery, Forestry, and related (401-461)	5	2.0	10	3.7
Processing (500-599)	10	4.0	17	6.4
Machine Trades (600-699)	14	5.6	30	11.2
Benchwork (700-795)	4	1.6	3	1.1
Structural Work (800-899)	61	24.6	44	16.5
Miscellaneous (900-979)	29	11.7	31	11.6
Total	248	100.0	267	100.0
Unknown:	4		2	
Unemployed, retired, on welfare, disabled, not applicable:	7		9	
Total	259		278	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C TABLE 97

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN A STRUCTURAL OCCUPATION

Husband employed in structural occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	61	24.6	44	16.5	1.65	1.07	2.55	5.22	< 0.05
No	187	75.4	223	83.5					
Total	248	100.0	267	100.0					
Unknown	4		2						
Not applicable, or unemployed	7		9						

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN A STRUCTURAL OCCUPATION BY SMOKING STATUS OF CASES AND COMPEERS

	Smoked cigarettes								
Husband employed in structural occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	55	23.2	22	13.8	1.90	1.10	3.26	5.46	< 0.05
No	182	76.8	138	86.3					
Total	237	100.0	160	100.0					
Unknown	10		6						
	Never smoked cigarettes								
Yes	6	54.5	22	20.6	4.64	1.29	16.61	6.37	< 0.05
No	5	45.5	85	79.4					
Total	11	100.0	107	100.0					
Unknown	1		5						
MANTEL-HAENSZIEL ODDS RATIO:					2.13	1.31	3.47	9.19	< 0.05

2063630922

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 98

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN A STRUCTURAL OCCUPATION, NO CASE OR COMPEER SIMILARLY EMPLOYED‡

Husband employed and no case or compeer in structural occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	61	24.6	43	16.2	1.69	1.09	2.62	5.65	< 0.05
No	187	75.4	223	83.8					
Total	248	100.0	266	100.0					
Unknown, not applicable:	11		11						

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN A STRUCTURAL OCCUPATION, NO CASE OR COMPEER SIMILARLY EMPLOYED‡, BY SMOKING STATUS OF CASES AND COMPEERS

Husband employed and no case or compeer in structural occupation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	55	23.2	21	13.2	1.99	1.15	3.44	6.13	< 0.05
No	182	76.8	138	86.8					
Total	237	100.0	159	100.0					
Unknown	10		6						
Never smoked cigarettes									
Yes	6	54.5	22	20.6	4.54	1.29	15.61	5.37	< 0.05
No	5	45.5	85	79.4					
Total	11	100.0	107	100.0					
Unknown	1		5						
MANTEL-HAENSZEL ODDS RATIO:					2.22	1.35	3.64	10.02	< 0.05

NOTE: No Case and only 1 Compeer was employed in a Structural Occupation whose husband had been usually employed in a Structural Occupation. The Compeer was a smoker.

‡ Dictionary of Occupational Titles code: 300 through 899.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 99

USUAL INDUSTRY OF HUSBAND OF LUNG CANCER CASES AND COMPEERS.

CATEGORIES OF INDUSTRIES	Cases No.	Cases %	Compeers No.	Compeers %
Agriculture, Forestry, and Fishing (0100-0971)	5	2.0	11	4.1
Mining (1000-1499)	17	6.9	18	6.7
Construction (1500-1799)	55	22.4	32	11.9
Manufacturing (2000-3999)	60	[illegible]		
Transportation, Communications, Electric, Gas and Sanitary Services (4000-4971)			29	10.7
Wholesale Trade (5000-5199)	15	6.1	18	6.7
Retail Trade (5200-5299)	14	5.7	26	9.6
Finance, Insurance, and Real Estate (6000-6799)	11	4.5	8	3.0
Services (7000-8999)	29	11.8	45	16.7
Public Administration (9100-9721	15	6.1	9	3.3
Total	246	100.0	270	100.0
Unknown:	8		4	
Unemployed,retired,on welfare, disabled, not applicable:	5		4	
Total	259		278	

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 100

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN THE CONSTRUCTION INDUSTRY

Husband employed in construction industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	55	22.4	32	11.9	2.14	1.33	3.45	10.14	< 0.05
No	191	77.6	238	88.1					
Total	246	100.0	270	100.0					
Unknown	8		4						
Not applicable, or unemployed	5		4						

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN THE CONSTRUCTION INDUSTRY BY SMOKING STATUS OF CASES AND COMPEERS

Husband employed in construction industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	49	20.9	16	9.9	2.40	1.31	4.40	9.47	< 0.05
No	186	79.1	146	90.1					
Total	235	100.0	162	100.0					
Never smoked cigarettes									
Yes	6	54.5	16	14.8	6.90	1.88	25.32	10.46	< 0.05
No	5	45.5	92	85.2					
Total	11	100.0	108	100.0					
Mantel-Haenszel odds ratio:					2.77	1.63	4.71	14.30	< 0.05
Unknown or not applicable:									
Smokers:	12		3						
Nonsmokers:	1		4						

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 101

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN THE CONSTRUCTION INDUSTRY, NO CASE OR COMPEER SIMILARLY EMPLOYED‡

Husband employed and no case or compeer in construction industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	54	22.0	31	11.5	2.17	1.34	3.51	10.27	< 0.05
No	191	78.0	238	88.5					
Total	245	100.0	269	100.0					
Unknown, not applicable:	13		8						

NOTE: One (1) Case and (1) Compeer was employed in the Construction Industry whose husband had a usual employment in the Construction Industry. Both had a history of smoking cigarettes.
‡ Standard Industrial Classification code: 1520 through 1799.

ODDS RATIO FOR EMPLOYMENT OF HUSBAND OF LUNG CANCER CASES AND COMPEERS IN THE CONSTRUCTION INDUSTRY, NO CASE OR COMPEER SIMILARLY EMPLOYED‡ BY SMOKING STATUS OF CASES AND COMPEERS

Husband employed and no case or compeer in construction industry	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	48	20.5	15	9.3	2.51	1.35	4.66	8.92	< 0.05
No	186	79.5	146	90.7					
Total	234	100.0	161	100.0					
Never smoked cigarettes									
Yes	6	54.5	16	14.8	6.90	1.88	25.32	10.46	< 0.05
No	5	45.5	92	85.2					
Total	11	100.0	108	100.0					
MANTEL-HAENSZEL ESTIMATE:					2.89	1.69	5.00	14.96	< 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 102

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO SMOKED CIGARETTES

Household member smoked	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	241	93.4	244	88.7	1.80	.97	3.34	3.56	n.s.†
No	17	6.6	31	11.3					
Total	258	100.0	275	100.0					

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO SMOKED CIGARETTES BY SMOKING STATUS OF CASES AND COMPEERS

	Household member smoked	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes	Yes	233	94.3	153	93.3	1.20	.53	2.70	.19	n.s.
	No	14	5.7	11	6.7					
	Total	247	100.0	164	100.0					
Never smoked cigarettes	Yes	8	72.7	91	82.0	.59	.14	2.41	.56	n.s.
	No	3	27.3	20	18.0					
	Total	11	100.0	111	100.0					
Mantel-Haenszel odds ratio:						1.01	.50	2.04	.01	n.s.

† n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 103

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN CEMENT MANUFACTURING

Household member worked in cement manufacturing	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	14	5.5	8	2.9	1.94	.80	4.70	1.81	n.s.
No	242	94.5	268	97.1					
Total	256	100.0	276	100.0					

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN CEMENT MANUFACTURING BY SMOKING STATUS OF CASES AND COMPEERS

Household member worked in cement manufacturing	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	12	4.9	3	1.8	2.78	.77	9.99	2.64	n.s.
No	232	95.1	161	98.2					
Total	244	100.0	164	100.0					
Never smoked cigarettes									
Yes	2	16.7	5	4.5	4.28	.73	24.96	3.03	n.s.
No	10	83.3	107	95.5					
Total	12	100.0	112	100.0					
Mantel-Haenszel odds ratio:					3.06	1.11	8.47	4.86	< 0.05

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 104

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN CEMENT MANUFACTURING, NO CASE OR COMPEER SIMILARLY EMPLOYED‡

Household member worked, no case or compeer, cement manufacture	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	14	5.5	7	2.5	2.21	.88	5.58	2.98	n.s.
No	242	94.5	268	97.5					
Total	256	100.0	275	100.0					

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN CEMENT MANUFACTURING, NO CASE OR COMPEER SIMILARLY EMPLOYED‡, BY SMOKING STATUS OF CASES AND COMPEERS

Household member worked, no case or compeer, cement manufacture	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	12	4.9	3	1.8	2.78	.77	9.99	2.64	n.s.
No	232	95.1	161	98.2					
Total	244	100.0	164	100.0					
Never smoked cigarettes									
Yes	2	16.7	4	3.6	5.35	.88	32.92	3.98	< 0.05
No	10	83.3	107	96.4					
Total	12	100.0	111	100.0					
MANTEL-HAENSZEL ESTIMATE:					3.19	1.15	8.85	4.95	< 0.05

NOTE: No case who lived with a Household Member employed in Cement Manufacture had been employed in the manufacture of cement, insulation or asbestos products. One (1) Compeer who lived with a Household member employed in Cement Manufacture had been employed in the Manufacture of Gaskets, Packing, and Sealing Devices. This Compeer had never smoked.

‡ Standard Industrial Classification codes: 2661, 3241, 3255, 3270 through 3275 and 3290 through 3299.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 105

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN HIGH RISE CONSTRUCTION

Household member worked high rise construction	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	29	11.3	13	4.7	2.56	1.30	5.05	6.99	< 0.05
No	227	88.7	261	95.3					
Total	256	100.0	274	100.0					
Unknown:	3		4						

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN HIGH RISE CONSTRUCTION BY SMOKING STATUS OF CASES AND COMPEERS

Household member worked high rise construction	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	27	11.1	8	4.9	2.41	1.07	5.45	4.71	< 0.05
No	217	88.9	155	95.1					
Total	244	100.0	163	100.0					
Never smoked cigarettes									
Yes	2	16.7	5	4.5	4.24	.73	24.73	2.98	n.s.
No	10	83.3	106	95.5					
Total	12	100.0	111	100.0					
Mantel-Haenszel odds ratio:					2.57	1.24	5.31	6.49	< 0.05
Unknown:									
Smokers	3		3						
Nonsmokers			1						

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 106

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN HIGH RISE CONSTRUCTION, NO CASE OR COMPEER SIMILARLY EMPLOYED‡

Household member worked high rise construction	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	27	10.6	13	4.7	2.39	1.20	4.74	6.52	< 0.05
No	227	89.4	261	95.3					
Total	254	100.0	274	100.0					
Unknown:	3		4						

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN HIGH RISE CONSTRUCTION, NO CASE OR COMPEER SIMILARLY EMPLOYED‡, BY SMOKING STATUS OF CASES AND COMPEERS

Household member worked high rise construction	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Smoked cigarettes									
Yes	25	10.3	8	4.9	2.23	.99	5.08	3.83	
No	217	89.7	155	95.1					
Total	242	100.0	163	100.0					
Never smoked cigarettes									
Yes	2	16.7	5	4.5	4.24	.73	24.73	2.98	n.s.
No	10	83.3	106	95.5					
Total	12	100.0	111	100.0					
MANTEL-HAENSZEL ESTIMATE:					2.41	1.16	5.01	5.52	< 0.05

NOTE: only 2 Cases and no Compeers were employed in High Rise Construction who had lived with a Household Member employed in High Rise Construction. The 2 Cases had a history of smoking cigarettes.

‡ Standard Industrial Classification codes: 1520 through 1542.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 107

ODDS RATIO FOR HISTORY OF FEMALE LUNG CANCER CASES AND COMPEERS HAVING LIVED WITH A HOUSEHOLD MEMBER WHO WORKED IN INSULATION MANUFACTURING

Household member worked in insulation	Cases No.	Cases %	Compeers No.	Compeers %	Odds Ratio	95% C.I. Low	95% C.I. High	Chi-Square	p Value
Yes	5	2.0	1	.4	5.52	.64	47.55	1.78	n.s.
No	251	98.0	277	99.6					
Total	256	100.0	278	100.0					

Unknown: 3

All cases and compeers who lived with a household member who worked in insulation manufacturing were smokers.

No Case or Compeer was employed in the Manufacture of Insulation, Cement, or Asbestos Products who had lived with a Household member employed in the Manufacture of Insulation (Standard Industrial Classification codes: 2661, 3241, 3255, 3270 through 3275, 3290 through 3299).

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 108

HISTOPATHOLOGIC TYPES OF CARCINOMA OF THE LUNG AMONG WHITE WOMEN BY AGE

Age group	Squamous cell carcinoma No.	%	Small cell carcinoma No.	%	Adeno-carcinoma No.	%	Large cell carcinoma No.	%	Adeno-squamous No.	%	Other carcinomas# No.	%	Unspecified†† carcinomas No.	%	All cell types No.	%
35 - 49 yr.	5	20.0	3	12.0	12	48.0	3	12.0					2	8.0	25	100.0
50 - 54 yr.	5	12.5	13	32.5	14	35.0							8	20.0	40	100.0
55 - 59 yr.	11	21.2	17	32.7	14	26.9	2	3.8			2	3.8	6	11.5	52	100.0
60 - 64 yr.	15	25.0	16	26.7	22	36.7	2	3.3					5	8.3	60	100.0
65 - 69 yr.	8	21.1	8	21.1	9	23.7	3	7.9	1	2.6			9	23.7	38	100.0
70 - 74 yr.	13	40.6	4	12.5	7	21.9	1	3.1	1	3.1			6	18.8	32	100.0
75 + yr.	4	33.3	1	8.3	5	41.7							2	16.7	12	100.0
Total	61	23.6	62	23.9	83	32.0	11	4.2	2	.8	2	.8	38	14.7	259	100.0

Squamous cell carcinoma: 8070.3
Small cell carcinoma: 8041.3 (N=15),8042.3 (N=47)
Adenocarcinoma: 8140.3 (N=73), 8250.3 (N=6), 8251.3 (N=1), 8260.3 (N=3)
Large cell carcinoma: 8012.3
‡ Fibrous histiocytoma: 8830.3, Carcinosarcoma: 8980.3
‡‡ 8000.3 (N=2) and 8010.3 (N=22) and 9980.8 (N=3) Carcinoma, NOS
8020.3 (N=11) Carcinoma undifferentiated, NOS

MAJOR HISTOPATHOLOGIC TYPES OF CARCINOMA OF THE LUNG AMONG WHITE WOMEN BY AGE

Age group	Squamous cell carcinoma No.	%	Small cell carcinoma No.	%	Adeno-carcinoma No.	%	All cell types No.	%
35 - 49 yr.	5	25.0	3	15.0	12	60.0	20	100.0
50 - 54 yr.	5	15.6	13	40.6	14	43.8	32	100.0
55 - 59 yr.	11	26.2	17	40.5	14	33.3	42	100.0
60 - 64 yr.	15	28.3	16	30.2	22	41.5	53	100.0
65 - 69 yr.	8	32.0	8	32.0	9	36.0	25	100.0
70 - 74 yr.	13	54.2	4	16.7	7	29.2	24	100.0
75 + yr.	4	40.0	1	10.0	5	50.0	10	100.0
Total	61	29.6	62	30.1	83	40.3	206	100.0

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 109

BASIS OF DIAGNOSIS OF FOUR MAJOR HISTOPATHOLOGIC CELL TYPES OF CARCINOMA OF THE LUNG AMONG WHITE WOMEN.

Basis of diagnosis	Squamous cell carcinoma No.	%	Small cell carcinoma No.	%	Adeno-carcinoma No.	%	Large cell carcinoma No.	%	All four cell type No.	%
Histology	49	27.7	52	29.4	66	37.3	10	5.6	177	100.0
Cytology	11	33.3	6	18.2	15	45.5	1	3.0	33	100.0
Autopsy	1	14.3	4	57.1	2	28.6			7	100.0
Total	61		62		93		11		217	

Squamous cell carcinoma: 8070.3
Small cell carcinoma: 8041.3 (N=15),8042.3 (N=47)
Adenocarcinoma: 8140.3 (N=73), 8250.3 (N=6), 8251.3 (N=1), 8260.3 (N=3)
Large cell carcinoma: 8012.3

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 110

HISTOPATHOLOGIC TYPES OF CARCINOMA OF THE LUNG AMONG WHITE WOMEN BY SMOKING STATUS

Smoking status	Squamous cell carcinoma No.	%	Small cell carcinoma No.	%	Adeno-carcinoma No.	%	Large cell carcinoma No.	%	Adeno-squamous No.	%	Other carcinomas‡‡ No.	%	Unspecified carcinomas‡ No.	%	All cell types No.	%
Smokers	58	23.5	61	24.7	76	30.8	11	4.5	2	.8	2	.8	37	15.0	247	100.0
Current	39	21.1	49	26.5	56	30.3	8	4.3	1	.5	1	.5	31	16.8	185	100.0
Exsmoker	19	30.6	12	19.4	20	32.3	3	4.8	1	1.6	1	1.6	6	9.7	62	100.0
Never	3	25.0	1	8.3	7	58.3							1	8.3	12	100.0
Total	61	23.6	62	23.9	83	32.0	11	4.2	2	.8	2	.8	38	14.7	259	100.0
Percent of cell types		23.6		23.9		32.0		4.2		.8		.8		14.7		100.0

Squamous cell carcinoma: 8070.3
Small cell carcinoma: 8041.3 (N=15),8042.3 (N=47)
Adenocarcinoma: 8140.3 (N=73), 8250.3 (N=6), 8251.3 (N=1), 8260.3 (N=3)
Large cell carcinoma: 8012.3
‡ 8000.3 (N=2), 8010.3 (N=22),8020.3 (N=11), 9980.8 (N=3)
‡‡ Fibrous histiocytoma: 8830.3, Carcinosarcoma: 8980.3

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 111

HISTOPATHOLOGIC TYPES OF CARCINOMA OF THE LUNG
AMONG WHITE WOMEN BY PACK-YEARS OF CIGARETTES SMOKED

Pack-years of cigarettes smoked	Squamous cell carcinoma No.	%	Small cell carcinoma No.	%	Adeno-carcinoma No.	%	All four cell types No.	%
1 - 16.42	13	32.5	7	17.5	20	50.0	40	100.0
16.43 - 34.21	6	25.0	9	37.5	9	37.5	24	100.0
34.22 - 43.80	15	30.0	19	38.0	16	32.0	50	100.0
65.71 +	21	30.4	20	29.0	28	40.6	69	100.0
Total	55	30.1	55	30.1	73	39.9	183	100.0

Squamous cell carcinoma: 8070.3
Small cell carcinoma: 8041.3 (N=13),8042.3 (N=42)
Adenocarcinoma: 8140.3 (N=68), 8250.3 (N=3), 8260.3 (N=2)

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

APPENDIX C, TABLE 112

ESTIMATES FOR ODDS RATIOS FOR EMPLOYMENT OF FEMALE LUNG CANCER CASES AND COMPEERS IN HIGH RISK INDUSTRIES AND/OR OCCUPATIONS BY SMOKING STATUS

Type of high risk employment*	Smoked cigarettes	High risk employment	Number of Cases	Number of Compeers	Odds Ratio	95% Confidence Interval Low	95% Confidence Interval High	Chi-Square	p Value
1.	Yes	Yes	161	102	9.20	4.40	19.66	42.01	< 0.05
	No	No	9	53					
1.	Yes	No	86	64	7.91	3.64	17.21	30.81	< 0.05
	No	No	9	53					
1.	No	Yes	3	59	.30	.08	1.16	4.52	< 0.05
	No	No	9	53					
2.	Yes	Yes	147	92	11.01	5.22	23.21	50.27	< 0.05
	No	No	9	62					
2.	Yes	No	100	74	9.31	4.35	19.93	39.18	< 0.05
	No	No	9	62					
2.	No	Yes	3	50	.41	.11	1.61	3.81	n.s.**
	No	No	9	62					
3.	Yes	Yes	79	42	13.17	6.46	28.82	59.11	< 0.05
	No	No	12	94					
3.	Yes	No	168	124	9.49	4.96	18.13	57.12	< 0.05
	No	No	12	94					
3.	No	Yes	9	28	.12	.01	2.07	4.33	< 0.05
	No	No	12	84					
4.	Yes	Yes	65	32	15.74	7.55	32.84	63.70	< 0.05
	No	No	12	93					
4.	Yes	No	182	134	10.53	5.54	19.99	65.76	< 0.05
	No	No	12	93					
4.	No	Yes	0	19	.19	.01	3.38	3.74	n.s.
	No	No	12	93					

* Type of high risk employment:
1. Employment in either a high risk industry or a high risk occupation.
2. Employment in a high risk industry.
3. Employment in a high risk occupation.
4. Employment in both a high risk industry and a high risk occupation.

** n.s. = not significant at the 5% level.

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Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

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RELATION OF FORCED EXPIRATORY VOLUME IN ONE SECOND (FEV_1) TO LUNG CANCER MORTALITY IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT)

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Kuller, L. H. (U. of Pittsburgh Graduate School of Public Health, Dept. of Epidemiology, Pittsburgh, PA 15261), J. Ockene, E. Meilahn, and K. H. Svendsen for the Multiple Risk Factor Intervention Trial Research Group. Relation of forced expiratory volume in one second (FEV_1) to lung cancer mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Epidemiol* 1990;132:265–74.

For men participating in the Multiple Risk Factor Intervention Trial, the authors evaluated the relation between the baseline forced expiratory volume in one second and lung cancer mortality among smokers between the third and tenth years of follow-up (1973–1974 to 1984). This measure of ventilatory function was a powerful predictor of lung cancer deaths, with rates that increased from 3.02 per 1,000 person-years in the lowest quintile of forced expiratory volume to 0.43 in the highest quintile. This relation was not weakened by adjustments for smoking dose, including number of cigarettes smoked per day, tar and nicotine content, duration of smoking, or age at onset of smoking. Nor was forced expiratory volume related to time between its determination and lung cancer death. If these observations can be verified in other studies, the forced expiratory volume in one second may identify smokers at very high risk of lung cancer and, hence, in need of more aggressive preventive approaches.

forced expiratory volume; neoplasms, lung; nicotine; smoking; tars

We have evaluated the relation between forced expiratory volume in one second (FEV_1) and lung cancer among cigarette smokers participating in the Multiple Risk Factor Intervention Trial (MRFIT). Cigarette smoking is a predominant risk factor for coronary heart disease (1), lung cancer (2), and chronic obstructive pulmonary disease (3). The risk of disease increases with dose of exposure to cigarette smoking measured as the duration of smoking, age at onset to current age, number of cigarettes smoked, type of cigarette, yield of tar or nicotine, presence or absence of a filter, and chemical measure of smoking exposure such as thiocyanate or cotinine (1–3).

Body size (height), increasing age, cigarette smoking, and possibly bronchial reactivity are the most important determinants of the levels of the FEV_1 (4, 5). There are also genetic, host susceptibility components to the levels of FEV_1 (4). Epidemiologic studies have repeatedly demon-

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Abbreviations: FEV_1, forced expiratory volume in one second; MRFIT, Multiple Risk Factor Intervention Trial.

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strated an inverse relation between levels of pulmonary function and risk of coronary heart disease death (6–9). A few studies have also reported an inverse relation between levels of pulmonary function and subsequent risk of lung cancer (10–12). The studies have been primarily limited to populations with existing pulmonary disease, relatively small sample sizes, or few measures of the dose of cigarette smoking.

Tockman et al. (10) determined the relative risk of lung cancer in relation to the level of FEV_1 in patients with chronic obstructive lung disease who participated in the Intermittent Positive Pressure Breathing Trial ($n = 676$) and in participants in the Johns Hopkins Lung Project ($n = 3,728$). The participants in the lung project were at high risk of lung cancer, had an average age of 45 years, and smoked at least one pack of cigarettes per day. A total of 22 participants died of lung cancer in the Intermittent Positive Pressure Breathing Trial, and 19 in the Johns Hopkins Lung Project. The risk of lung cancer was substantially increased among those with impaired pulmonary function defined as an FEV_1 of less than 60 percent of that expected, compared with the Johns Hopkins Lung Project participants who had a forced expiratory volume of 85 percent or greater and no shortness of breath or bronchitis. The Intermittent Positive Pressure Breathing Trial participants with a forced expiratory volume of less than 60 percent of that predicted had a 4.85-fold increased risk of lung cancer, and the participants in the Johns Hopkins Lung Project with impaired pulmonary function had a 2.7-fold increased risk. Neither bronchitis nor shortness of breath was a risk factor for lung cancer. The lung cancer risk appeared to be linearly increased with declining pulmonary function. The increased risk of lung cancer and decreasing pulmonary function was not substantially modified by adjusting for age, pack-years of smoking, or bronchitis history. The risk of lung cancer associated with decreased pulmonary function was substantially greater than that for pack-years of smoking.

Skillrud et al. (11) studied 113 persons with decreased pulmonary function forced expiratory volume of less than 70 percent of the predicted normal value and 113 control persons with an FEV_1 of greater than 85 percent of that predicted. Persons were followed from 1973–1974 to 1984. Lung cancer developed in nine cases and two controls ($p = 0.024$). The cases and controls were matched for the amount smoked, age, and occupation.

Davis (12) followed up 835 patients at the Bellevue Emphysema Clinic in New York who had an average age of 60 years. The incidence of lung cancer was 11.6/1,000 person-years. The rates of lung cancer were estimated to be substantially higher than those reported for other studies of smokers (12).

Materials and Methods

MRFIT was a randomized primary prevention trial designed to test the effects of a multifactorial intervention on mortality from coronary heart disease in high-risk men selected on the basis of their levels of diastolic blood pressure, serum cholesterol, and number of cigarettes smoked (13). Clinical follow-up of the participants, including an intervention program for men in the special intervention group ended on February 28, 1982. Continued mortality surveillance of the trial participants through December 31, 1985, resulted in an average follow-up of 10.5 years. The design and results for the 10.5 years of follow-up have previously been presented (14).

Of the 12,866 men in the trial, 6,428 were randomized to special intervention and 6,438 to usual care between December 1973 and February 1976. They were aged 35–57 years at entry. Approximately 92 percent were white.

Prior to randomization, the men were evaluated at three visits. At the initial visit, the number of cigarettes currently smoked was the only measure of smoking reported, and 8,194 (63.7 percent) men reported currently smoking cigarettes. At the second visit for those eligible, serum thiocyanate (a chemical measure of smoking dose (15)), a physical examination, and pulmonary function were performed. At the third visit, a more detailed smoking history was conducted, including measurements of smoking dose, number of cigarettes smoked, age at onset of smoking, and tar and nicotine content of cigarettes. The smokers averaged 34 cigarettes per day at the first visit. The average age at onset of smoking was 18 years, and approximately half of the men began smoking between the ages of 16 and 19 years.

Men who had a serious life-shortening disease or who were believed to be unable to participate in the specific interventions were excluded from the trial prior to randomization. Most individuals with clinically significant chronic obstructive pulmonary disease, as well as those with documented clinical myocardial infarction or angina pectoris, or electrocardiogram evidence of an old myocardial infarction were probably excluded prior to randomization. Of the randomized participants who smoked cigarettes, 85 reported a history of emphysema and 504 reported a history of asthma.

During the trial and after termination of clinical follow-up in 1982, the vital status of each man was checked by clinical center staff. Since February 28, 1982, vital status has been determined using the National Death Index and information provided by the Social Security Administration. Mortality ascertainment using these data sources through December 31, 1985 is estimated to be 100 percent complete (14). Through February 28, 1982, a Mortality Review Committee classified specific causes of deaths by reviewing hospital records, autopsy reports, and information from physicians and next-of-kin. From March 1982 through 1985, only the death certificates were available for review.

Pulmonary function was initially measured during the examination at the second visit prior to randomization and annually thereafter. Pulmonary function techniques and quality control procedures have been described in detail (16). The pulmonary function measurements were completed using a 10-liter Stead-Wells water-filled spirometer (Stead-Wells, Braintree, MA). Standardization of pulmonary function measurements and calibration checks were not given high priority in 1972 at the start of the trial and prior to development of standardization guidelines. A rigid standardization program was introduced several years into the trial, and prior pulmonary function tracings were carefully reviewed using standardized criteria. The specific criteria have been described in detail (16). The quality of the forced expiratory tracings was rated using four criteria: 1) abruptness of takeoff, 2) completeness of exhalation, 3) smoothness of exhalation and 4) absence of fast starts (16). These criteria met standards subsequently developed by the American Thoracic Society (17) and the Epidemiology Standardization Project (18). The plastic tubes of the spirometer were checked each week for leakage. Only 57 percent of the baseline tracings (7,368 of 12,866) met our criteria based on reviews of the tracings as satisfactory for analysis. There were no differences in baseline characteristics between men with and those without acceptable tracings at baseline (9). By year three of the study (table 1), approximately 85 percent of the tracings had met the acceptable criteria for the study. The FEV_1 measurements were also adjusted for temperature.

The pulmonary function results in this paper are based on third-year data because of the lesser number of acceptable tracings at baseline. These results therefore exclude from the analysis men who died before year three, those who did not attend the third-year visits, and those with unacceptable tracings (table 1).

There were 12,866 participants in the MRFIT trial. Approximately 64 percent

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TABLE 1

Number of lung cancer, coronary heart disease, and all-cause deaths after year 3 for MRFIT cigarette smokers at first visit by completion of the pulmonary function test at year 3, 1973–1974 to 1985*

Status of pulmonary function test	Lung cancer		Coronary heart disease deaths	Death any cause
	No.	No. of Deaths		
Missed test	932	18 (2.65)†	27 (3.97)	105 (15.45)
Unacceptable tracing	1,073	11 (1.35)	34 (4.16)	80 (9.79)
Acceptable tracing	6,075	60 (1.31)	196 (4.29)	468 (10.24)

* MRFIT, Multiple Risk Factor Intervention Trial.
† Numbers in parentheses, rate per 1,000 person-years.

(8,194 men) were cigarette smokers at their first screening examination. Among the 8,194 smokers, 114 had died through year three, leaving 8,080 smokers at the third annual examination. The lifetime nonsmokers were excluded because there were no lung cancers among them. The exsmokers at entry were also excluded because the smoking history prior to the trial, especially the amount smoked and the time of smoking cessation prior to the study, was probably not as accurate as for the smokers in the trial. Of the remaining 8,080 smokers, satisfactory pulmonary function measurements were available for 6,075 (75 percent) (table 1). The high mortality for lung cancer and total mortality among those who did not have a test at year three is explained by annual visits missed because of chronic illness between entry into trial and the third-year examination. There were 119 deaths from lung cancer over 10.5 years of follow-up (table 2). The number of lung cancer deaths among cigarette smokers at entry was similar between the usual care (50 deaths) and special intervention (56 deaths) groups.

Seventeen of the 106 lung cancer deaths among cigarette smokers occurred during the first three years of follow-up and are not included in further analysis of the third year FEV_1 and subsequent risk of lung cancer. There were 47 deaths in the special intervention group and 42 in the usual care group after year three. The results of the FEV_1 analysis are based on 60 of the 89 subsequent lung cancer deaths from year three to year 10.5, for which there were good FEV_1 measurements at the third-year examination (table 1). As noted, there was no significant difference in baseline characteristics for those with and those without acceptable tracings.

The dose of smoking was evaluated by the number of cigarettes, age at onset, and tar and nicotine content of the cigarettes. The thiocyanate levels in blood were the only chemical measure of smoking dose. Certain foods may raise the thiocyanate levels. Diuretics may also increase thiocyanate levels. However, among smokers, thiocyanate is an excellent measure of smoking dose (15).

The FEV_1 was inversely correlated with the number of cigarettes smoked, thiocyanate levels, and age, and was directly correlated with height. All four of these variables were also related to total mortality. Statistical analysis, therefore, included adjustment for these confounding variables.

The statistical methods used in the MRFIT trial have been described in detail in previous publications (13). Rates are given as number of events per 1,000 person-years of observation. The relation between FEV_1 and smoking and other variables was assessed using the Cox proportional hazards model (19). The tests for linear trends were performed using the Cox model with number of cigarettes per day and other risk factors as covariates. The estimate of relative risks in the multiple regression analysis is based on techniques described in the paper by Kahn and Sempos (20).

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RESULTS

The levels of the FEV_1 were divided into five quintiles among the cigarette smokers (table 3). As expected, FEV_1 was related to the measures of smoking dose, including number of cigarettes smoked, thiocyanate, and age at onset of smoking (table 3). Neither smoking of filter cigarettes nor tar content was related to FEV_1.

The FEV_1 was an independent predictor

TABLE 2

Lung cancer deaths and mortality rates per 1,000 person-years by number of cigarettes smoked per day at first examination, MRFIT, 1973–1974 to 1985*

	Total	Lung cancer deaths	
		No.	Rate/1,000 person-years
Never smokers	1,859	0	0
Ex-smokers	2,513	13	0.43
Smokers at first screening (no. of cigarettes/day)	8,194	106	1.29
1–19	856	2	0.22
20–39	3,747	50	1.29
≥40	3,591	54	1.45
p value for linear trend among smokers†			<0.001

* MRFIT, Multiple Risk Factor Intervention Trial.
† From Cox proportional hazards model (19) using the number of cigarettes smoked per day as a covariate.

TABLE 3

Mean values of selected baseline variables for MRFIT first screen smokers by FEV_1 quintile at year 3 examination, 1973–1974 to 1985*

Variable	Quintile I (≤2,670 ml)		Quintile II (2,671–3,051 ml)		Quintile III (3,052–3,376 ml)		Quintile IV (3,377–3,748 ml)		Quintile V (≥3,749 ml)	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Age (years)	48.8	5.5	47.3	5.4	46.0	5.7	44.6	5.5	42.2	5.2
No. of cigarettes/day at first visit	35.2	14.8	34.0	15.3	33.7	15.2	33.5	15.9	32.5	15.2
Thiocyanate (μmol/liter)	171.1	55.5	171.2	58.6	168.1	58.1	165.5	59.1	161.1	58.9
Age at which smoking began (years)	17.2	3.9	17.6	4.2	17.6	4.0	18.0	4.0	18.1	4.3
% filter cigarettes	78		84		85		83		85	
Tar (mg)	19.0	4.6	18.4	4.5	18.2	4.5	18.4	4.6	18.3	4.6
Nicotine (mg)	1.2	0.3	1.2	0.3	1.2	0.3	1.2	0.3	1.2	0.3
Alcoholic drinks/week	13.1	12.7	13.3	12.4	13.6	12.6	13.3	11.6	14.7	13.3
Diastolic blood pressure (mm)	97.2	8.1	97.5	8.0	96.7	5.1	96.6	7.8	96.7	7.9
Cholesterol (mg)	246.1	40.2	248.9	38.7	252.4	38.9	249.9	39.1	251.8	37.8

* MRFIT, Multiple Risk Factor Intervention Trial; FEV_1, forced expiratory volume in one second.

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of lung cancer mortality over the approximate 7.5 years of follow-up after the year three examination (table 4). The relation was linear and was weakened only slightly by adjustment for the number of cigarettes smoked per day, age, height, and other variables.

We evaluated the relation between several other measures of smoking dose and lung cancer. The thiocyanate level was directly related to lung cancer mortality among the cigarette smokers. Neither the level of nicotine nor tar content of cigarettes smoked at baseline was significantly related to lung cancer deaths (21). This is probably due to the narrow range and relatively low levels of tar, with 58 percent of the 8,194 men who smoked at the first screening examination smoking cigarettes with 16–19 mg of tar. There was also a very narrow range of age at onset of smoking and no relation between age at onset and lung cancer mortality (21).

In a previous report, Townsend (22) evaluated the effects of smoking cessation on the FEV_1 decline at three of the MRFIT centers. Those who had stopped smoking experienced a smaller rate of decline of FEV_1 during the trial than those who continued to smoke. The difference was about 22 ml/year. Thus, it is unlikely that smoking cessation during the trial would substantially shift individuals within quintiles of the FEV_1 that differ by about 350 ml.

Men who stopped smoking during the trial did not have a lower lung cancer mortality rate than those who continued to smoke. Among the 945 men in the special intervention group who stopped smoking at year one, 10 (10.6/1,000 men) died of lung cancer as compared with 35 (12.7/1,000 men) among the 2,754 men in the special intervention group who continued to smoke. The number who stopped smoking was much smaller for the usual care group, and there was also no reduction in lung cancer mortality among the ex-smokers in the group. Smoking cessation is not a likely confounder of the relation between the FEV_1 and lung cancer in this study (21).

There was a possibility that the FEV_1/lung cancer relation might be due to a shorter time period between the measurement of the FEV_1 at year three and subsequent lung cancer death. Among the 27 lung cancer deaths in the lowest quintile of FEV_1, the mean number of days between the FEV_1 measurement and lung cancer death was 1,680, while for the four deaths in the highest quintile it was 1,504 days.

TABLE 4

MRFIT lung cancer deaths and mortality rates by FEV_1 quintiles at year 3 for smokers at first visit, 1973–1974 to 1985*

FEV_1 (ml)	No. of cigarettes smoked at time of first visit	No. of lung cancer deaths	Relative risk	95% confidence interval	Adjusted† relative risk	95% confidence interval
≤2,670	1,208	27 (3.02)‡	1.0		1.0	0.33–1.39
2,671–3,051	1,211	12 (1.33)	0.44	0.22–0.87	0.68	0.37–1.63
3,052–3,376	1,217	15 (1.64)	0.54	0.29–1.02	0.78	0.37–1.63
3,377–3,748	1,220	2 (0.22)	0.07	0.02–0.30	0.14	0.03–0.62
≥3,749	1,219	4 (0.43)	0.14	0.05–0.40	0.28	0.06–1.06
p value for linear trend			<0.001		<0.001	

* MRFIT, Multiple Risk Factor Intervention Trial; FEV_1, forced expiratory volume in one second.

† Adjusted for baseline covariates: age, height, number of cigarettes smoked per day, thiocyanate, age at which smoking began, use of filter cigarettes, tar and nicotine content, alcoholic drinks/week, diastolic blood pressure, and cholesterol.

‡ Numbers in parentheses, rate per 1,000 person-years.

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TABLE 5

Relative risk and regression coefficients from the Cox proportional hazards model (19) for the endpoint lung cancer death after the third year of follow-up for MRFIT screen 1 smokers, 1973–1974 to 1985*

Variable	Adjusted relative risk	*p* value	Difference associated with relative risk
Age (years)	1.08	0.005	Per single year of age
No. of cigarettes/day at time of first visit	1.58	0.027	Per 20 cigarettes
FEV_1 at third annual examination	0.49	0.001	Increase 1,000 ml

* MRFIT, Multiple Risk Factor Intervention Trial; FEV_1, forced expiratory volume in one second.

Only four of the 27 lung cancer deaths in the lowest quintile occurred within 2 years of the FEV_1 measurements and none within one year, while 12 occurred more than 5 years after the year three FEV_1 measurements.

The Cox proportional hazards linear regression model included age, cigarettes smoked, thiocyanate levels, age at which smoking began, use of filter or nonfilter cigarettes, tar and nicotine content, alcohol consumption, diastolic pressure, cholesterol levels, and height. Only age, number of cigarettes smoked per day, and the third annual FEV_1 were significant predictors of subsequent lung cancer mortality (table 5). There is clearly a high correlation among the smoking variables, especially number of cigarettes smoked, thiocyanate level, and age at onset of smoking. The important observation, however, was that the FEV_1 was independently related to the risk of lung cancer adjusted or unadjusted for the variables, including both the smoking variables and some of the other risk factors for selection in MRFIT (15). Further analysis of each of these variables separately did not demonstrate a strong relation with lung cancer except FEV_1, number of cigarettes smoked, and thiocyanate.

History of symptoms of chronic bronchitis, such as cough in the morning during the winter and phlegm, was measured at the annual examination using standardized respiratory symptom questionnaires (23). The symptoms increased with the dose of cigarette smoking. For example, cough in the morning in the winter increased in frequency from 5 percent among noncigarette smokers to 14 percent in those who smoked 1–14 cigarettes per day to 64 percent among men who smoked 45 or more cigarettes per day. There was an increased risk of lung cancer among cigarette smokers who reported respiratory symptoms as compared with no symptoms (table 6). In the multivariate Cox proportional hazards regression model, only the presence of phlegm in the winter for greater than 3 months was a significant predictor of lung cancer after adjustment for age, smoking dose, and FEV_1. The relation of FEV_1 with lung can-

TABLE 6

Relation between symptoms and reported disease for smokers at first visit and lung cancer/1,000 person-years, 1973–1974 to 1985

	No.	Rate	Relative risk
Cough on winter morning			
Yes	3,786	1.66	1.9
No	4,407	0.89	1.0
Cough night or day			
>3 months/year	2,555	1.93	2.1
≤3 months/year	702	1.09	1.2
No	4,927	0.91	1.0
Phlegm			
>3 months	2,586	1.75	1.9
≤3 months	892	1.30	1.3
No	4,722	0.95	1.0
Emphysema			
Yes	85	5.9	4.9
No	8,109	1.2	1.0
Asthma			
Yes	504	1.33	1.1
No	7,687	1.24	1.0
Bronchitis			
Yes	1,444	1.46	1.2
No	6,745	1.20	1.0

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

cer mortality was, however, not substantially affected by including the incidence of winter phlegm for greater than 3 months in the regression analysis (table 7). There was no relation between reported shortness of breath and subsequent lung cancer mortality.

There also was no relation between a history of asthma and bronchitis at entry into the trial and subsequent 10.5-year lung cancer mortality among the cigarette smokers (table 6). There were five deaths (5.9/1,000 person-years) due to lung cancer among the 85 men who had a history of emphysema and 101 (1.2/1,000 person-years) among the 8,109 without such a history.

Discussion

The FEV_1 was an independent predictor of lung cancer in this study. There were no lung cancer deaths among never-smokers, and therefore, the relation between FEV_1 and lung cancer cannot be tested independent of cigarette smoking.

The prior determinants of ventilatory function in a population are age, height, smoking, airway responsiveness, various measures of environmental pollutants, infection, and genetic factors (24). Height was not a risk factor for lung cancer, and therefore, did not influence the relation of FEV_1 to lung cancer.

The age range within the MRFIT, 35–57 years, was relatively narrow, and the results were age-adjusted. Of the 106 lung cancer deaths, 56 occurred in the group aged 50–57 years at entry. Even limiting the analysis to rates within the group aged 45–57 years at entry and age-adjusting within this narrow age band did not modify the association of lung cancer with FEV_1.

Limited occupational data are available. Many of the occupational lung cancers reported in the literature are confounded by cigarette smoking, either as an additive or a multiplicative interaction (25). The MRFIT included 22 different centers in the United States. No detailed analysis of MRFIT data regarding the relation of occupation and lung cancer has been published. It is unlikely, however, that a strong interaction of high-risk occupations with FEV_1 would account for the relation of FEV_1 and lung cancer seen in this study. There is relatively little evidence that environmental pollution (26, 27) is an important risk factor for lung cancer compared with cigarette smoking at the present time.

The first National Health and Nutrition Examination Survey follow-up study (28) reported a relative risk of 1.02 for developing any cancer among persons with a history of asthma. The prevalence of asthma (5.7 percent) was similar to that in MRFIT (6 percent). There was no relation between asthma and lung cancer among the small group that reported asthma at entry in MRFIT. The risk of lung cancer associated with only allergies in the National Health and Nutrition Examination Survey was 1.19, which was also not significant. Detailed allergy history was not available in MRFIT, but is unlikely to be the explanation for the relation of low FEV_1 and lung cancer.

TABLE 7

Proportional hazards general linear regression model for lung cancer deaths, MRFIT, 1973–1975 to 1985*

	Adjusted relative risk	*p* value	*p* (excluding phlegm >3 months)	Difference associated with relative risk
Age (years)	1.10	0.000	0.000	Per single year of age
No. of cigarettes/day at time of first visit	1.61	0.012	0.003	Per 20 cigarettes
FEV_1 year 3	0.60	0.008	0.002	Increase 1,000 ml
Winter phlegm for >3 months	3.38	0.04		

* MRFIT, Multiple Risk Factor Intervention Trial; FEV_1, forced expiratory volume in one second.

The association of FEV_1 and lung cancer could be due to any of the following: 1) FEV_1 is a better measure of exposure to carcinogens in cigarette smoke than the usual history of smoking exposure; 2) Individuals with decreased FEV_1 are at further increased risk of lung cancer because of inability to clear carcinogens from the respiratory tract; 3) Decreased FEV_1 is a measure of a combination of aging and carcinogenic exposure, since both age and smoking are the primary determinants of the level of FEV_1; and 4) There was a shared genetic liability to both lung cancer and decreased pulmonary function.

It is possible that the rate of decline in the FEV_1 due to aging, independent of the smoking dose, may partially explain the relation between it and lung cancer mortality. A study in non-cigarette smokers may be necessary in order to clarify the independent effect of aging on the FEV_1 and the risk of disease.

The genetic susceptibility hypothesis (29) has been based on the heredity of pulmonary function (30, 31) and the apparent increased risk of lung cancer, possibly independent of smoking dose, among relatives of patients with chronic obstructive pulmonary disease (32). The confounding of smoking dose may weaken this hypothesis. There are a few studies that report familial aggregation of lung cancer (33–35), but most do not include good smoking histories within and between families.

The most plausible hypothesis is that low FEV_1 is a marker of exposure to carcinogens in cigarette smoking. It is also a predictor of coronary heart disease and total mortality (9). The relation with coronary artery disease is much weaker than for lung cancer. Combining FEV_1 and smoking history may identify a group of smokers at an unusually high risk of lung cancer.

Smoking cessation is the only known approach to reducing the risk of lung cancer substantially and probably also to reducing the rate of decrease of pulmonary function, including the FEV_1, with age among smokers (22, 36). In neither situation can the prior damage due to cigarette smoking be completely eliminated by smoking cessation (4, 37).

The number of lung cancer deaths and the mortality rates will remain high for the foreseeable future because of the large population of current and ex-smokers, especially among high-risk older individuals (38). Identification of smokers and ex-smokers with lower FEV_1 may provide a population at highest risk in which more aggressive smoking cessation interventions, especially more costly individualized approaches, tests of chemopreventive agents such as beta-carotene or retinoids (39), and evaluation of new screening techniques (40) for early detection of lung cancer are needed.

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PARENTAL OCCUPATION AND INTRACRANIAL NEOPLASMS OF CHILDHOOD: RESULTS OF A CASE-CONTROL INTERVIEW STUDY

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Wilkins, J. R., III (Dept. of Preventive Medicine, Ohio State U., Columbus, OH 43210–1240), and T. Sinks. Parental occupation and intracranial neoplasms of childhood: results of a case-control interview study. *Am J Epidemiol* 1990;132:275–92.

In 1983–1984, the authors conducted a case-control study of environmental factors and childhood brain tumor risk. Cases (n = 110) were identified through the tumor registry of a pediatric hospital and matched controls (n = 193) through random digit dialing. In addition to parental occupational histories, telephone interviews elicited information about potential confounders and hypothesized risk factors for childhood brain tumors. Relying primarily on the Hoar et al. (*J Occup Med* 1980;22:722–6) job-exposure matrix, the authors examined parental employment characteristics in relation to the relevant developmental periods. Paternal employment in several industries (agriculture, construction, metal, and food and tobacco) and in several occupations (agriculture, benchwork, and transportation) was associated with excess risk. The range of notably elevated odds ratios was 2.0–3.3, with all confidence intervals including 1.0 except one. Elevated but unstable odds ratios were also found for both paternal and maternal employment in jobs "clustered" together because of common exposures. For both approaches to exposure classification, the greatest excess risks were consistently demonstrated for parental jobs held in the preconception period. Job-exposure matrix analyses indicated that case fathers were more likely than control fathers to have had jobs linked with aromatic amino and aromatic nitro compounds (range of notably elevated (and unstable) odds ratios, 3.4–4.4), but here the greatest excess risks were exhibited in the postnatal period. Few associations emerged for maternal employment characteristics, although this is probably explained by the relatively small number of women employed in jobs outside the home.

brain neoplasms; carcinogens, environmental; child; environmental exposure; occupational medicine

Epidemiologic studies of parental occupation and childhood cancer date back to 1974, when Fabia and Thuy (1) reported a twofold excess risk of cancer death among children less than 5 years of age whose fathers had jobs classified as "hydrocarbon-related." Since then, the relevant literature has grown considerably (2–37).

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Abbreviations: CI, confidence interval; OR, odds ratio.

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The Relationship of Smoking Cessation to Coronary Heart Disease and Lung Cancer in the Multiple Risk Factor Intervention Trial (MRFIT)

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Abstract: The impact of smoking cessation on coronary heart disease (CHD) and lung cancer was assessed after 10.5 years of follow-up in the 12,866 men in the Multiple Risk Factor Intervention Trial (MRFIT). Those men who died of lung cancer (n = 119) were either cigarette smokers at entry or ex-smokers; no lung cancer deaths occurred among the 1,859 men who reported never smoking cigarettes. The risk of lung cancer for smokers, adjusted for selected baseline variables using a Cox proportional hazards model, increased as the number of cigarettes smoked increased (B = 0.0203, SE = 0.0076). There was not the same graded response for CHD among smokers at entry. The risk of CHD death was greater among smokers than nonsmokers (RR = 1.57) (B = −0.0034, S.E. = 0.0048). After one year of cessation, the relative risk of dying of CHD for the quitters as compared to non-quitters (RR = 0.63) was significantly lower even after adjusting for baseline differences and changes in other risk factors. The relative risk for smokers who quit for at least the first three years of the trial was even lower compared to non-quitters (RR = 0.38). However, the relative risk for lung cancer for quitters versus non-quitters was close to 1 both for quitters at 12 months and at three years. These data support the benefits of cessation in relation to CHD and are consistent with other epidemiologic studies which suggest that the lag time for a beneficial effect of smoking cessation on lung cancer may be as long as 20 years. (*Am J Public Health* 1990; 80:954–958.)

Introduction

In the last two decades there have been continuing decreases in coronary heart disease (CHD) mortality rates in all United States populations[1–3] while lung cancer mortality rates continue to increase in certain populations.[4,5] Epidemiologic studies have consistently demonstrated a significantly higher relative risk for smokers compared to former smokers for each of these diseases.[1,2,6–8]

The beneficial effect of smoking cessation on CHD is rapid; as the period of cessation increases, the ex-smoker's relative risk approaches that of the never smoker.[3] However, in one study this return occurred gradually over a 20-year period.[8] The relative risk of developing lung cancer has been demonstrated to decrease as the period of cessation increases for smokers who have stopped smoking,[6–8] but their relative risk is still significantly elevated after 10 to 20 years of cessation compared to lifetime never smokers and is related to both the duration of smoking and length of cessation.[6–8]

In the available studies, the effect of smoking cessation on the risk of developing CHD and lung cancer was estimated either using data gathered retrospectively[6–8] or by considering that smoking habits were unchanged over the period of follow-up.[6,7] It is likely that during the course of these studies some ex-smokers became current smokers and vice versa. In addition, use of retrospective data entails problems of recall, and reports of cessation during the course of follow-up of these studies were not validated with biochemical measures. As a result, the mortality ratios reported for ex-smokers may be too high, and the benefits for cessation may actually be greater than those previously demonstrated for lung cancer and for CHD.

Using the detailed smoking behavior data gathered prospectively in the Multiple Risk Factor Intervention Trial (MRFIT), biochemically validated with serum thiocyanate measurements, we evaluated the relationship of smoking cessation to the development of CHD and lung cancer among middle-aged men, after 10.5 years of follow-up.

Methods

The MRFIT[9–21] was sponsored by the National Heart, Lung and Blood Institute (NHLBI) as a clinical trial, to test the effect of a multifactor intervention program on mortality from CHD. Other objectives included examination of decreases in other mortality and morbidity end points including lung cancer. In summary, the participants were 12,866 men ages 35–57 years at increased risk for CHD and free of overt CHD on entry. Men were designated at increased risk if their levels of the three major CHD risk factors—serum cholesterol, cigarette smoking, and blood pressure—were high enough at first screening to place them in the top 15 percent (later changed to 10 percent for 72 percent of the men screened) of a risk score distribution based on data from the Framingham Heart Study. Men with diastolic blood pressure of 115 mmHg or higher and those with total cholesterol of 350 mg/dl or higher were excluded.

Of the 12,866 men randomized to the special intervention (SI) and usual care (UC) groups, 64 percent (n = 8194) reported smoking cigarettes at the initial screening examinations, an average of 33.9 cigarettes/day. Randomization occurred from December 1973 to February 28, 1976. Thus, on February 28, 1982, when active intervention was terminated, each surviving man had been in the trial for at least six years, with a mean duration of 6.9 years of follow-up from randomization.

All SI men were encouraged and helped to make dietary changes directed at lowering their blood cholesterol levels. The smoking intervention program used an initial intensive group approach as well as individual counseling sessions when indicated. Both approaches included the use of behavioral and cognitive interventions. SI men who were hypertensive (mean diastolic blood pressure greater than or equal to 90 mm Hg on two consecutive visits, or on antihypertensive medication from their personal physicians) were treated with a stepped care approach.[13,18] UC men were not offered

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intervention at the clinical centers and were referred back to their usual source of medical care. They were asked to return to the MRFIT clinical center once a year for a comprehensive evaluation, including assessment of risk factors and morbidity status.

Baseline and annual data collection for both groups during the trial included a medical history and examination, information on past smoking patterns, and reported present cigarettes per day. Serum thiocyanate (Scn) was also measured at baseline and annually to validate reported smoking status. In addition to cigarette smoking, Scn may be elevated by the use of pipes, cigars and cigarillos, certain foods and diuretics.[22] Subjects with an Scn level of more than 100 μ mols/L were assessed to be smoking.

Mortality Ascertainment

During the trial and at termination of active intervention on February 28, 1982, deaths were ascertained by clinic staff through contact with family or friends of the deceased, routine follow-up of missed clinic visits, response to postcards requesting change-of-address information sent twice yearly to UC participants, and searches of publicly accessible files of deceased persons. The main source of vital status information after completion of participation in February 1982 has been the Social Security Administration and the National Death Index. Mortality ascertainment through December 31, 1985 was estimated to be approximately 100 percent complete using these data sources.[18]

The cause of death used in this report is based on death certificate reports. Cause-specific death rates are based on coding of death certificates by trained nosologists, according to the Ninth Revision of the International Classification of Diseases (ICD-9).[23] Each death certificate was independently coded by two nosologists and disagreements were adjudicated by a third nosologist. ICD-9 codes 410 to 414 and 429.2 were used to identify CHD deaths; ICD-9 code 162 was used to identify lung cancer deaths.

Statistical Methods

The SI-UC differences for the end points CHD and lung cancer mortality were tested for statistical significance using the log-rank test.[24] As in other MRFIT publications, 90 percent confidence intervals for the percentage difference in death rates are presented. Mortality rates are presented as number of cases per 1,000 person-years.

The relationship between smoking-related variables and end points was assessed for the combined MRFIT SI and UC smokers at entry into the study using the cox proportional hazards model.[25,26] In one analysis, smokers at entry who attended the first annual examination were classified as *quitters* if they reported not smoking at the first annual examination and had serum Scn levels that were less than 100 μ mols/L, or as *smokers*. In other analyses, smokers at entry who attended the first three annual examinations were classified as *persistent quitters, if at each of the three annual* examinations they reported not smoking and had serum Scn levels which were less than 100 μ mols/L at each visit, or as *other smokers/quitters*.

Relative risk (RR) estimates and 95 percent confidence intervals for quitters compared to non-quitters were calculated using the proportional hazards regression model. RRs are presented both unadjusted and adjusted for age, baseline blood pressure, cholesterol, number of cigarettes smoked per day, and years of education (as an index of socioeconomic status) added to the model as continuous variables. Differences in baseline characteristics and changes in risk factor levels from baseline to the third annual examination for persistent quitters compared to other smokers/quitters were tested for statistical significance using Student's t test.

Results

As of December 31, 1985, after an average period of follow-up of 10.5 years, there were 1,033 deaths in the MRFIT. There were 146 CHD deaths (3.42/1,000 person-years) among the SI smokers at entry and 165 (3.89/1,000 person-years) among the UC smokers at entry, a relative difference of −12.1 percent (90% CI = −27.1, 5.9). The CHD mortality rates were 2.26/1,000 person-years and 2.44/1,000 person-years for SI and UC non-smokers at entry, respectively. There were 56 lung cancer deaths (1.31/1,000 person-years) among the SI smokers at entry and 50 (1.18/1,000 person-years) among the UC smokers at entry, a relative difference of +11.3 percent (90% CI = −19.2, 53.3). The nine SI and four UC non-smokers at entry who died of lung cancer had been smokers at some point prior to entry into the study.

Mortality in Subgroups Defined after Randomization

Although smoking intervention in the MRFIT resulted in a significantly higher cessation rate for SI compared to UC men ($p < .001$), the lung cancer and CHD mortality rates were not significantly different for these two groups. (Smoking cessation results in the MRFIT will be presented in detail in a subsequent section.) The within group analyses presented in Tables 1–5 are observational, combining data for SI and UC participants.

No lung cancer deaths occurred among the 1,859 MRFIT men who had never smoked cigarettes. Among cigarette smokers there appeared to be a graded relationship between the number of cigarettes smoked per day at baseline, and the lung cancer mortality rate. However, number of cigarettes smoked per day at baseline and risk of CHD mortality did not appear to have as strong a relationship as for lung cancer. Ex-smokers appeared to have a risk of dying from CHD that approached that of never smokers (Table 1).

In the MRFIT study group, never smokers had higher cholesterol and/or blood pressure levels than smokers at baseline in order to be in the top 10 percent of CHD risk. Regression analyses to account for confounders shown in Tables 2 and 3 indicate that only age, the screen 1 cigarettes/day, and baseline Scn are of importance for lung cancer; for CHD mortality age, baseline Scn, DBP, and cholesterol were all significant risk factors ($p < 0.01$). Removing Scn from the regression analysis did not result in a significant relationship between number of cigarettes smoked and CHD risk among smokers.

TABLE 1—CHD and Lung Cancer Deaths and Mortality Rates per 1,000 Person-Years by Number of Cigarettes Smoked per Day at Baseline for MRFIT SI and UC Men Combined

		CHD Deaths		Lung Cancer Deaths	
	Total	N	Rate/1000 Person-Years	N	Rate/1000 Person-Years
Never-smokers	1859	44	2.22	0	0
Ex-smokers	2813	73	2.44	13	0.43
Smokers*					
1–19	856	23	2.56	2	0.22
20–39	3747	173	4.45	50	1.29
≥40	3591	115	3.08	54	1.45

*Number of cigarettes/day smoked

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TABLE 2—Regression Coefficients from Cox Proportional Hazards Model for the End Point Lung Cancer Death for MRFIT SI and UC Men Who Reported Smoking Cigarettes at Entry

Variables	Coefficient	SE
Age (years)	0.1239	0.0198
Screen 1 cigarettes/day	0.0203	0.0076
Serum Thiocyanate (μmoles/l)	0.0041	0.0019
Age began smoking (years)	−0.0147	0.0270
Filter/non-filter (1 = filter, 0 = non-filter)	−0.6440	0.4076
Tar	−0.1334	0.0952
Nicotine	1.9110	1.3438
Alcoholic drinks/week	−0.0120	0.0090
Screen 1 DBP (mmHg)	0.0153	0.0155
Screen 1 cholesterol (mg/dl)	−0.0025	0.0030

TABLE 3—Regression Coefficients from the Cox Proportional Hazards Model for the End Point CHD Death for MRFIT SI and UC Men who Smoked Cigarettes at Entry

Variables	Coefficient	SE
Age (years)	0.0626	0.0104
Screen 1 cigarettes/day	−0.0034	0.0048
Serum Thiocyanate (μmoles/l)	0.0029	0.0011
Age began smoking	−0.0127	0.0154
Filter/non-filter (1 = filter, 0 = non-filter)	−0.3337	0.2447
Tar	0.0489	0.0567
Nicotine	−0.9942	0.7927
Alcoholic drinks/week	−0.0150	0.0055
Screen 1 DBP (mmHg)	0.0317	0.0091
Screen 1 cholesterol (mg/dl)	0.0047	0.0017

CHD and lung cancer mortality rates for all men who quit smoking during the first year were compared with the rates of those who continued to smoke (Table 4). The total group of smokers who reported quitting in year one and had Scn <100 μ mols/L had a relative risk of dying from CHD .63 that of non-quitters. The relative risk estimate adjusted for entry risk variables were similar to unadjusted estimates (Table 4). The quitters had the same lung cancer mortality rate from year one to the end of the trial as those who were non-quitters at year one (Table 4). (This was true regardless of baseline levels of smoking or whether they were in the UC or SI group.)

TABLE 4—Number of CHD and Lung Cancer Deaths and Mortality Rate (per 1,000 person-years) from the 12-month visit through 12/31/85[a] for Baseline Smokers by Smoking Status at 12 months, and Relative Risk Estimates (Quitters/Not Quitters) for MRFIT SI and UC Men

Smoking Status	# of Participants SI + UC	Deaths SI + UC	Relative Risk Quit/Not Quit (95% CI)	Adjusted Relative Risk[d] (95% CI)
		Coronary Heart Disease		
Quit[b]	1365	33 (2.54)[c]	.63 (.44,.90)	.58 (.40,.84)
Not Quit	6298	239 (4.04)		
		Lung Cancer		
Quit[b]	1365	17 (1.31)[c]	0.99 (.59,1.67)	1.05 (.62,1.79)
Not Quit	6298	78 (1.32)		

[a] This represents an average of 9.5 years of followup
[b] Quitters are S_1 smokers who reported no smoking at year 1 with SCN <100 μ moles/L.
[c] Rates per 1000 person-years.
[d] Adjusted for age, baseline cigarettes/day, cholesterol, blood pressure, education

We also looked at persons who had quit smoking for at least the first three years of the trial (persistent quitters). Compared to the continuing smokers, the persistent quitters experienced a reduced risk of CHD death (RR = .38) but no change in risk of dying of lung cancer (Table 5). These comparisons are limited by the small number of quitters who persisted for three years which was less than the number who persisted for one year. (Participants who died in the first three years of the trial are also not included.) Persistent quitters were also lighter smokers than those who did not persist (average 30.1 vs 34.2 cigarettes per day).

Persistent quitters and continuing smokers had differences in baseline risk factors and in changes in other risk factors through the three years the two groups were compared. On average, persistent quitters smoked four fewer cigarettes per day and drank 2.2 fewer alcoholic drinks per week at baseline than did other smokers or short-term quitters. Persistent quitters experienced significantly greater weight gain by three years than other smokers or quitters. Adjusting for the differences in risk factors at baseline did not change the relative risk estimates (0.38 versus 0.35), nor did adjusting for the differences in risk factor changes (RR = 0.36, 95% CI = 0.20, 0.65). Likewise, none of these models produced changes in relative risk estimates for lung cancer.

The distribution of lung cancer deaths throughout the span of the trial does not indicate any difference in early versus late mortality by randomization status. Therefore, there is no evidence to date for a trend toward fewer SI as compared to UC lung cancer deaths as time from entry becomes longer, or closer to the 10.5 year maximum follow-up. Because of the relatively small number of participants who were long-term quitters of three or more years and died of lung cancer, it is not possible to evaluate whether the lung cancer death rates might be declining in the latter years of the trial among persistent quitters.

Cessation and Relapse Patterns

Although CHD and lung cancer mortality rates were not significantly different between the randomized groups, smoking cessation rates were significantly different for SI compared to UC men (Figure 1). The cross-sectional data indicate that, throughout the six years of follow-up in the trial, cessation rates for SI smokers were approximately 17 percentage points greater than they were for UC smokers.

TABLE 5—Number of CHD and Lung Cancer Deaths and Mortality Rate (per 1,000 person-years) from the 36-month visit through 12/31/85[a] for Baseline Smokers by Smoking Status at 36 months, and Relative Risk Estimates (Quitters/Not Quitters) for MRFIT SI and UC Men

Smoking Status	# of Participants SI + UC	Deaths SI + UC	Relative Risk Quit/Not Quit (95% CI)	Adjusted Relative Risk[d] (95% CI)
		Coronary Heart Disease		
Quit[b]	908	12 (1.72)[c]	0.38 (.21, .68)	0.35 (.20,.63)
Not Quit	6035	205 (4.52)		
		Lung Cancer		
Quit[b]	908	9 (1.29)[c]	.96 (.48,1.93)	1.02 (.50,2.05)
Not Quit	6035	61 (1.34)		

[a] This represents an average of 7.5 years of followup
[b] Quitters are S_1 smokers who reported no smoking at years 1, 2 and 3 with Scn <100 μ moles/L.
[c] Rates per 1000 person-years
[d] Adjusted for age, baseline cigarettes/day, cholesterol, blood pressure, education

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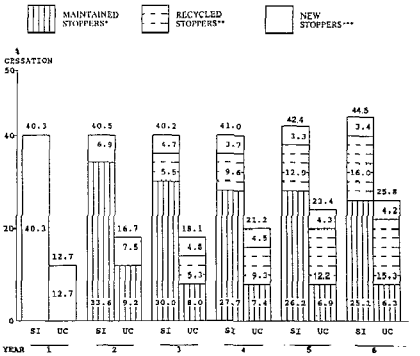

If missed visit then participant is assumed smoking.
Cessation rates are adjusted for death.
*Smokers who maintained cessation from year one to the noted year of follow-up.
**Smokers who stopped, relapsed and stopped again; or smokers who stopped after year one and remained off cigarettes.
***Smokers who had not previously reported cessation in the trial but stopped after noted annual examination.

FIGURE 1—Distribution of Smoking Cessation History for Each Annual Visit for Special Intervention(SI) and Usual Care(UC) Smokers.
***Smokers who maintained cessation from year one to the noted year of follow-up.**
****Smokers who stopped, relapsed and stopped again; or smokers who stopped after year one and remained off cigarettes.**
*****Smokers who had not previously reported cessation in the trial but stopped after noted annual examination.**

(Reported rates are used in Figure 1 because by year six there was very little discrepancy between the reported rates and the rates validated by serum Scn.) Cross sectional data do not indicate what proportion of smokers stopped and continued off for the duration of the trial. Cohort data (vertical striped bar) indicate that 25 percent of the SI smokers (60 percent of those who quit in year one) remained abstinent through year six of the trial. For the UC smokers, 6.9 percent (54 percent of those who quit in year one) remained abstinent through year six.

The three groups—maintained stoppers, recycled stoppers, and new stoppers—were calculated for light (<25 cigarettes/day) versus heavy (≥25 cigarettes/day) smokers for the SI and UC groups, respectively. There were lower cross-sectional cessation rates among heavy smokers compared to light smokers in both the SI and UC groups; an approximately two-fold difference in maintained cessation rates for light versus heavy smokers; and a four-fold difference for SI versus UC smokers. For example, only 19.4 percent of SI heavy smokers stayed off of cigarettes for the six years of the trial and only 5.2 percent of UC heavy smokers did so.

Discussion

Smoking cessation during the trial had a substantial and fairly rapid beneficial effect on CHD mortality. The lack of an observable beneficial effect of stopping smoking on lung cancer at the 10.5 year follow-up may in part reflect the long lag period associated with the development of lung cancer. The MRFIT data are consistent with observational studies of lung cancer and smoking cessation indicating that the effect of smoking cessation is related to length of cessation and that there is still a substantial increase in risk for lung cancer among former smokers even after relatively long periods of cessation when compared to never-smokers.[6–8] Given that the MRFIT smoking data were prospectively collected, biochemically validated, and substantially more precise than data from any previous epidemiologic study, they strengthen previous evidence reflecting the immediate beneficial effect of smoking cessation on CHD and the long lag period with respect to a potential beneficial effect on lung cancer.

The sample size estimate for the MRFIT was based on CHD end points and changes in multiple risk factors. Therefore, it was not designed to detect the specific effect of smoking cessation nor differences in lung cancer mortality, which has a lower incidence than CHD mortality. The 90 percent confidence interval bounds for the +11.3 percentage point difference in lung cancer mortality rates for SI compared to UC smokers ranged from −9.2 to +53.3 percent. It is therefore unlikely that a substantial effect (i.e., greater than 20–30 percent lower lung cancer mortality for SI smokers), was missed due to lack of power.

To our knowledge, the MRFIT is only the second intervention trial which has examined the relationship between lung cancer mortality and smoking in randomized groups. The first such trial was the Whitehall Civil Servants Smoking Intervention Trial carried out by Rose and his colleagues.[27] After 10 years of follow-up, there were 22 lung cancer deaths in the intervention group and 25 in the normal care group. Intervention subjects (N = 714) reported a significant net decrease of 7.6 cigarettes/day compared to the control subjects (N = 731) after nine years of follow-up. This trial did not have adequate power to detect a difference in lung cancer. In addition, no objective measures of smoking were obtained. There are no data available from this trial with regard to persistence of quitting or cessation and maintenance rates for heavy versus lighter smokers.

The data confirm results from studies indicating an overwhelming smoking effect on lung cancer risk, with a greater relative risk for heavier smokers as compared to lighter smokers.[1,2,4,6–8] We found no effect of tar or nicotine levels on lung cancer either by univariate or multivariate analysis, suggesting that smokers should not develop a false sense of security by switching to lower tar and nicotine cigarettes.

In previous analysis, we have shown that dose of smoking is an important CHD risk factor when MRFIT smokers and ex-smokers are combined.[13,18] However, the number of cigarettes smoked per day at entry had little effect on risk for CHD when the analysis was limited to smokers only. In part, this is due to the multifactorial etiology of CHD, and may also be related to the focus of MRFIT recruitment on high-risk men, yielding a skewed distribution with a preponderance of relatively heavy smokers. Using a multivariate Cox Proportional Hazard model, baseline Scn level, which is a better marker of acute dose of exposure to cigarettes than reported number of cigarettes smoked, had a significant effect on CHD risk among smokers.

Quitters tended to gain more weight than non-quitters. However, the differences were modest and did not affect the relative risk estimates for CHD of quitters compared to non-quitters when included in the model. CHD deaths did occur among never-smokers, also confirming the multifactorial etiology of CHD.[3,28–34] By the nature of the MRFIT inclusion criteria, those individuals who were non-smokers on entry into the trial had relatively higher levels of serum cholesterol and blood pressure.

In most studies, a large number of persistent quitters is not available to adequately test the relationship of smoking

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cessation to reduction in death rates; and most persistent quitters are lower risk, lighter smokers. This lack of persistent quitters is likely to attenuate the relationship between cessation and risk. If many years of persistent quitting is required to produce a beneficial effect on lung cancer mortality rates, it will be difficult to carry out studies to demonstrate such an effect.

The disparity in the beneficial effects of smoking cessation observed in this study between lung cancer and CHD mortality may help to explain the disparity seen nationally between sharply decreasing CHD mortality rates and lung cancer mortality rates which show little change. The greater smoking prevalence in earlier birth cohorts also accounts in part for the persistent high lung cancer death rates in these older individuals. Furthermore, some older smokers may have avoided cardiovascular death by smoking cessation and may now be at high risk of lung cancer, further increasing the pool of lung cancer susceptibles.

Lung cancer continues to be a major public health problem. Prevention of smoking and cessation at the youngest possible age for those individuals already smoking are the most important determinants of the future trends of lung cancer mortality.

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LEE, P.N.

"TRENDS IN LUNG CANCER, CHRONIC OBSTRUCTIVE LUNG DISEASE, AND EMPHYSEMA DEATH RATES FOR ENGLAND AND WALES 1941-85 AND THEIR RELATION TO TRENDS IN CIGARETTE SMOKING"

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PREVENTIVE MEDICINE 20, 638–654 (1991)

Cigarette Smoking and Mortality[1]

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Methods. The relationship of cigarette smoking and smoking cessation to mortality was investigated among men screened for and also among those randomized to the Multiple Risk Factor Intervention Trial (MRFIT).

Results. Among the 361,662 men screened for the MRFIT, cigarette smoking was an important risk factor for all-cause, coronary heart disease (CHD), stroke, and cancer mortality. These risks, on the log relative scale, were strongest for cancers of the lung, mouth, and larynx. The excess risk associated with cigarette smoking was greatest for death from CHD. Overall, approximately one-half of all deaths were associated with cigarette smoking. Among the 12,866 randomized participants, weak positive associations with duration of cigarette smoking habit and tar and nicotine levels were found with all-cause mortality. For both SI and UC men, substantial differences in subsequent CHD (34–49%) and all-cause (35–47%) mortality were evident for men who reported cigarette smoking cessation by the end of the trial compared with those continuing to smoke. There was no evidence that lung cancer death rates were lower among cigarette smokers who quit compared with those who continued to smoke in this 10-year follow-up period.

Conclusion. The data are consistent with results of previous epidemiologic studies indicating that the benefits of smoking cessation on CHD are rapid, while for lung cancer, the benefit is not evident in a 10-year follow-up period. © 1991 Academic Press, Inc.

INTRODUCTION

Major prospective studies completed in the 1960s and 1970s contributed substantially to our understanding of the relationship between smoking and disease (1). These studies provided estimates of relative and attributable risk associated with cigarette smoking. Relative risks for smokers compared with nonsmokers were greater for smoking-related cancers and chronic obstructive pulmonary disease than for coronary heart disease (CHD); however, of these smoking-related diseases, mortality due to CHD accounted for over one-third of the excess deaths due to cigarette smoking.

Since the 1960s, there have been relatively few longitudinal studies that have measured the effects of cigarette smoking on health. Most studies have had relatively small sample sizes and have focused primarily on cardiovascular disease (CVD) endpoints, such as CHD or stroke. At the present time, there are only four large longitudinal studies in the United States that are evaluating the effects of smoking on a variety of disease endpoints: the Nurses' Health Study (2), the follow-up of the participants in the National Health and Nutrition Examination Survey (3), the American Cancer Society's volunteer study (4), and the follow-up of men screened for the Multiple Risk Factor Intervention Trial (MRFIT) (5,6).

[1] Address reprint requests to the Coordinating Centers for Biometric Research, 2221 University Avenue S.E., Suite 200, Minneapolis, MN 55414-3080.

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Previously Reported Results for 361,662 Men Screened for the MRFIT

Prior reports based on the men screened for the MRFIT have noted:

(a) A clear dose relationship between cigarette smoking and both CHD and total mortality after 5 years among black and white men (6). The relationship between smoking and CHD mortality was stronger for the younger (35 to 44 years) than for older age (55 to 57 years) groups on the log relative scale but excess risk attributable to smoking was greater in the older age group (8).

(b) A significant association between cigarette smoking and stroke (6, 9).

(c) An increased risk of CHD mortality among diabetics who smoked cigarettes compared with nonsmoking diabetics (10).

(d) A strong association between cigarette smoking and mortality due to chronic obstructive pulmonary disease (11).

(e) The additive effects of smoking, cholesterol level, and blood pressure on CHD mortality (6).

Previously Reported Results for 12,866 Randomized Participants

Prior reports for randomized participants have also indicated a strong relationship among cigarette smoking, CHD, total mortality, and incident myocardial infarction (12, 13). There was also a clear and striking dose–response relationship between the number of cigarettes smoked and lung cancer mortality (14). Cigarette smokers had decreased forced expiratory volume at 1 sec (FEV_1) at entry to the trial and a greater decline in the FEV_1 over time as compared with former smokers or those who had never smoked (15). Decreased pulmonary function was also associated with increased cancer mortality among smokers (14). Low levels of beta-carotene or carotene in serum among cigarette smokers was an independent predictor of lung cancer (16).

Results from the first 7 years of follow-up in the MRFIT showed that while there was no difference in total mortality between the SI and UC participants, SI men experienced a 7% lower CHD death rate than UC men (5). After 10.5 years of follow-up, mortality rates were lower for SI men than UC men by 10.6% for CHD and by 7.7% for all causes (17). Men who had quit smoking in both the SI and UC groups had lower CHD and total mortality and a reduced incidence of nonfatal coronary events after 7 years of follow-up compared with those who continued to smoke (5, 12).

The purpose of the current investigation is threefold: (a) to study the relationship of cigarette smoking with total and cause-specific mortality in the large cohort of men screened for MRFIT in the 1970s, thus providing updated information on the risks of cigarette smoking; (b) to examine the relationship between mor-

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tality and the tar and nicotine content of cigarettes smoked by the men randomized to MRFIT; and (c) to compare the mortality experience of men who quit smoking with that of those who did not.

METHODS

Participants were selected for the trial from among 361,662 men age 35–57 years screened in 22 clinical centers in the United States, based on a combination of their cigarette smoking habits, diastolic blood pressure (DBP), and serum cholesterol levels at screen 1. A risk score was calculated using a logistic regression function derived from Framingham men in the same age group (18). Initially, men in the upper 15% and subsequently those in the upper 10% of risk were selected. Detailed descriptions of selection criteria data collected at the three screening visits (screen 1, screen 2, and screen 3) and intervention results are given elsewhere (5, 19–21).

Proportional hazards regression models were used to evaluate the association between cigarette smoking and subsequent mortality (22) and to compare mortality rates for the SI and UC groups. Measures of smoking dose were divided into three or more categories and adjusted relative risks were estimated for each category relative to the first. In addition, analyses which treated measures of smoking dose as continuous variables and which compared all smokers versus nonsmokers were also performed. Baseline covariates included in regression models are footnoted in the tables. Cause-specific mortality was based on death certificates coded by trained nosologists using the Ninth Revision of the International Classification of Diseases (23).

RESULTS

Men Screened for MRFIT

Among the 361,662 men seen at the initial screening visit in the MRFIT, 133,117 (37%) reported smoking an average of 26 cigarettes per day. Mortality results for men screened were consistent with results from studies reported in the 1960s—significant associations between cigarette smoking and major causes of death were evident (Table 1). Smoking remained a powerful risk factor for cancers of the lung, pancreas, mouth, larynx, esophagus, kidney, and bladder and for total cancer deaths, as well as for CHD, stroke, and total mortality. Risks for smokers relative to nonsmokers ranged from greater than 6 for cancers of the lung, mouth, and larynx to 2–2.5 for other causes of death (Table 1). Overall, cigarette smoking was associated with 1,776 excess deaths from CHD and 4,856 excess deaths from all causes (50.5% of all deaths among cigarette smokers). These risk estimates associated with cigarette smoking are probably conservative since, based on the initial screen data, former smokers cannot be separated from those who never smoked cigarettes. It is also not known how many non-cigarette smokers smoked pipes, cigars, or cigarillos.

Randomized Participants

At screen 1, approximately 64% of the 12,866 randomized participants reported smoking an average of 33 cigarettes per day. Approximately 20% of participants

TABLE 1
TEN-YEAR AGE-ADJUSTED MORTALITY RATES (PER 10,000 MEN) BY REPORTED CIGARETTE SMOKING STATUS FOR MEN SCREENED IN THE MRFIT

Endpoint (ICD-9 codes)	Nonsmoker[a] (n = 238,345)		Cigarettes/day 1–15 (n = 27,858)		16–25 (n = 44,840)		26–35 (n = 20,730)		36–45 (n = 23,396)		46+ (n = 8,293)		Adjusted relative risk (smoker/nonsmoker)[b]	Coefficient for cigarettes/day[c]
	No. deaths	Rate per 10,000	No. deaths	Rate per 10,000	No. deaths	Rate per 10,000	No. deaths	Rate per 10,000	No. deaths	Rate per 10,000	No. deaths	Rate per 10,000		
All-cause mortality	8,426	357.2	1,495	558.5	3,127	723.1	2,250	896.9	1,999	985.2	742	950.1	2.2*	0.0233*
CHD (410–414, 429.2)	2,973	125.5	535	202.3	1,157	267.2	832	309.7	629	304.8	239	305.8	2.1*	0.0228*
Stroke (430–438)	262	11.1	59	22.1	119	27.4	84	31.4	57	27.2	17	20.9	2.5*	0.0241*
All cancers (140–239)	2,690	113.8	423	159.0	1,029	239.3	761	288.4	751	341.5	265	370.2	2.4*	0.0268*
Lung (162)	436	19.2	130	49.5	479	111.8	371	140.4	411	188.0	157	205.1	6.7*	0.0465*
Pancreas (157)	172	7.3	24	9.0	69	16.1	40	15.6	35	16.0	9	10.5	2.0*	0.0198*
Mouth and pharynx (140–149, 161)	35	1.5	9	3.4	30	7.0	24	9.5	39	17.5	16	21.1	6.6*	0.0500*
Esophagus (150)	73	3.1	15	5.6	29	6.7	17	6.3	18	8.2	12	15.9	2.4*	0.0289*
Kidney (189)	113	4.8	11	4.1	30	7.0	34	12.9	23	10.6	8	10.1	1.9*	0.0256*
Bladder (188)	39	1.6	5	1.8	13	3.1	12	4.4	9	3.9	3	3.6	2.0**	0.0247*

[a] Includes exsmokers at first screen.
[b] Adjusted for age, diastolic blood pressure, serum cholesterol level, and race (black nonblack).
[c] Regression coefficient for cigarettes/day in a model with age, diastolic blood pressure, serum cholesterol level, and race (black/nonblack) in the model. The coefficients for cigarettes/day are all significant at the 0.0001 level.
* $P < 0.0001$.
** $P < 0.002$.

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smoked more than 45 cigarettes per day. The percentage of smokers was much higher among younger (age, <45 years; 71% smokers) compared with the older randomized participants (age, ≥45 years; 59% smokers) (7).

The association between the number of cigarettes smoked and other smoking-related variables, such as serum SCN and the age the participant began smoking cigarettes, is presented in Table 2. Over 80% of cigarette smokers smoked filter cigarettes. Tar and nicotine levels averaged 18.6 and 1.2 mg, respectively, and varied little according to the number of cigarettes smoked. The average age at which participants began smoking was approximately 18 years, with 25% of participants starting to smoke before age 16. Heavy smokers began smoking at an earlier age than light smokers. The average SCN for cigarette smokers was 168.2 μmol/liter, ranging from 113.6 μmol/liter for those smoking 1–15 cigarettes per day to 187.5 μmol/liter for those smoking >45 cigarettes per day.

A detailed smoking history was obtained for randomized participants at screen 3. Causes of death for SI and UC participants by smoking status (current and former smokers and those who had never smoked) at screen 3 are summarized in Table 3. Within each smoking category, none of the differences between SI and UC participants was significant. For all participants, regardless of smoking status, mortality rates were lower for SI than for UC groups by 10.6% (one-sided $P = 0.12$) for CHD and by 7.7% (one-sided $P = 0.10$) for all-cause mortality.

Consistent with the findings for all men screened, randomized cigarette smokers were at increased risk of death from CHD, lung cancer, and total mortality compared with nonsmokers (Table 4). Adjusted risk ratios for those who smoked 26 cigarettes per day or more compared with nonsmokers were 2.6 (95% CI: 2.0 to 3.4), 7.2 (95% CI: 3.8 to 13.7), and 2.7 (95% CI: 2.3 to 3.2) for CHD, lung cancer, and total mortality, respectively. Death rates for those smoking 1–25 cigarettes per day were also significantly greater than those for nonsmokers. There was not a single death due to lung cancer among participants who reported never smoking cigarettes (24).

There was a strong relationship between the serum SCN levels, another measure of smoking dose, and the risk of mortality among cigarette smokers (Table 5). The adjusted risks for the highest relative to the lowest quintile of SCN among cigarette smokers were 2.2, 3.3, and 2.5 for CHD, lung cancer, and total mortality, respectively (Table 5).

To study the association between the duration of the smoking habit and the risk of death, participants were classified by age at the time of screening (35–44 and 45–57 years) and age when they began smoking (Table 6). The majority of men began smoking between 15 and 19 years of age; thus, most men age 35–44 at initial screening had been smoking for 15 to 30 years and men age 45–57 had been smoking for 25 to 40 years. There was only weak evidence that the initial age of daily smoking was related to CHD and lung cancer mortality. Among men age 35–44 years at randomization, there was a borderline significant inverse association between the initial age of daily smoking and total mortality ($P = 0.06$), but this association was not evident for men age 45–57. Both the nicotine and the tar contents of the cigarettes smoked at entry were modestly associated with the risk of death (Tables 7 and 8).

TABLE 2

RELATIONSHIP BETWEEN NUMBER OF CIGARETTES SMOKED PER DAY AT SCREEN 1 AND SELECTED BASELINE CHARACTERISTICS OF MRFIT RANDOMIZED PARTICIPANTS

	Reported number of cigarettes/day													
	1–15		16–25		26–35		36–45		>45		All smokers			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%		
Type of cigarette														
Filter	693	86.1	1,403	80.9	1,642	81.1	1,689	81.6	1,277	83.8	6,704	82.2		
Nonfilter	112	13.9	331	19.1	383	18.9	380	18.4	247	16.2	1,453	17.8		
Tar														
≤15	75	11.2	149	9.6	251	13.4	275	14.3	242	16.9	992	13.3		
16–19	436	65.0	912	58.7	1,065	56.8	1,101	57.2	833	58.0	4,347	58.3		
>20	160	23.8	492	31.7	559	29.8	549	28.5	360	25.1	2,120	28.4		
Mean (SD)	18.4	(4.2)	19.0	(4.3)	18.6	(4.7)	18.5	(4.8)	18.0	(4.9)	18.6	(4.6)		
Nicotine														
≤1.0	154	23.0	300	19.3	446	23.8	465	24.2	412	28.7	1,777	23.8		
1.1–1.4	423	63.0	961	61.9	1,075	57.3	1,110	57.7	794	55.3	4,363	58.5		
≥1.5	94	14.0	292	18.8	354	18.9	350	18.2	229	16.0	1,319	17.7		
Mean (SD)	1.2	(0.3)	1.2	(0.3)	1.2	(0.3)	1.2	(0.3)	1.2	(0.3)	1.2	(0.3)		
Age began smoking														
≤15	125	15.5	347	20.0	497	24.5	596	28.8	500	32.8	2,065	25.3		
16–17	181	22.5	486	28.0	583	28.8	589	28.5	403	26.4	2,242	27.5		
18–19	209	26.0	447	25.8	479	23.7	435	21.0	306	20.1	1,876	23.0		
20–21	129	16.0	251	14.5	251	12.4	233	11.3	165	10.8	1,029	12.6		
22–23	53	6.6	77	4.4	100	4.9	111	5.4	61	4.0	402	4.9		
≥24	108	13.4	126	7.3	115	5.7	106	5.1	89	5.8	544	6.7		
Mean (SD)	19.2	(5.11	18.0	(4.0)	17.6	(3.8)	17.3	(3.8)	17.1	(4.2)	17.7	(4.1)		
Thiocyanate quintile (μmol/liter)														
<122	471	59.0	452	26.7	283	14.4	217	10.8	168	11.3	1,591	20.0		
123–156	155	19.4	428	25.3	438	22.3	340	17.0	217	14.6	1,578	19.9		
157–183	88	11.0	341	20.1	400	20.3	434	21.7	292	19.7	1,555	19.6		
184–213	49	6.1	275	16.2	463	23.6	484	24.2	359	24.2	1,630	20.5		
≥214	36	4.5	197	11.6	382	19.4	528	26.4	448	30.2	1,591	20.0		
Mean (SD)	113.6	(53.0)	153.7	(53.0)	173.2	(53.2)	183.0	(53.0)	187.5	(56.5)	168.2	(58.2)		

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TABLE 3

NUMBER OF DEATHS (AND PERCENTAGE OF NUMBER RANDOMIZED) BY CAUSE FOR MRFIT SI AND UC PARTICIPANTS AT 10.5 YEARS OF FOLLOW-UP BY REPORTED SCREEN 3 SMOKING STATUS

Cause of death	ICD-9 code	Never smoked cigarettes			Exsmokers			Smokers		
		SI (n = 931)	UC (n = 928)	% difference[a]	SI (n = 1394)	UC (n = 1419)	% difference[a]	SI (n = 4103)	UC (n = 4091)	% difference[a]
All cardiovascular	390–459	31 (3.33)	31 (3.34)	−0.7	38 (2.73)	52 (3.66)	−25.8	197 (4.80)	207 (5.06)	−5.3
CHD	410–414, 429.2[b]	23 (2.47)	21 (2.26)	11.2	33 (2.37)	40 (2.82)	−17.2	146 (3.56)	165 (4.03)	−11.7
Cerebrovascular	430–438	4 (0.43)	5 (0.54)	—	3 (0.22)	4 (0.28)	—	13 (0.32)	14 (0.34)	−5.9
Other CVD		4 (0.43)	5 (0.54)	—	2 (0.14)	8 (0.56)	—	38 (0.93)	28 (0.68)	32.2
All noncardiovascular		23 (2.47)	17 (1.83)	37.2	35 (2.51)	38 (2.68)	−2.5	171 (4.17)	191 (4.67)	−11.4
Neoplastic	140–239	10 (1.07)	9 (0.97)	—	23 (1.65)	23 (1.62)	6.1	107 (2.61)	117 (2.86)	−9.4
Respiratory and intrathoracic organs	160–165	0 (0.00)	0 (0.00)	—	9 (0.65)	4 (0.28)	—	57 (1.39)	51 (1.25)	11.2
Lung	162	0 (0.00)	0 (0.00)	—	9 (0.65)	4 (0.28)	—	56 (1.36)	50 (1.22)	11.6
Other neoplasms		10 (1.07)	9 (0.97)	—	14 (1.00)	19 (1.34)	−21.1	50 (1.22)	66 (1.61)	−25.3
Respiratory	460–519	4 (0.43)	1 (0.11)	—	1 (0.07)	3 (0.21)	—	8 (0.19)	12 (0.29)	—
Digestive system	520–579	4 (0.43)	2 (0.22)	—	2 (0.14)	3 (0.21)	—	16 (0.39)	11 (0.27)	46.0
Accidents, suicides, homicides	800–999	5 (0.54)	4 (0.43)	—	6 (0.43)	7 (0.49)	—	27 (0.66)	32 (0.78)	−17.0
Other non-CVD		0 (0.00)	1 (0.11)	—	3 (0.22)	2 (0.14)	—	13 (0.32)	19 (0.46)	−32.5
Cause unknown (death certificate not found)		0 (0.00)	0 (0.00)	—	0 (0.00)	0 (0.00)	—	1 (0.02)	1 (0.02)	—
Total		*54 (5.80)*	*48 (5.17)*	*12.6*	*73 (5.24)*	*90 (6.34)*	*−16.1*	*369 (8.99)*	*399 (9.75)*	*−8.2*

Note. ICD, International Classification of Diseases; SI, special intervention; UC, usual care; CVD, cardiovascular disease; CHD, coronary heart disease. Dashes signify less than 10 deaths in SI or UC groups; therefore, the percentage difference is not displayed.

[a] Defined as (RR-1) × 100%; RR estimated from proportional hazards regression model. None of the differences are significant at the 0.05 level.

[b] Cardiovascular disease, unspecified with use of Ninth Revision, coded as 412.4 with use of Eighth Revision.

TABLE 4

RELATIONSHIP BETWEEN NUMBER OF CIGARETTES SMOKED AT SCREEN 1 AND CHD, LUNG CANCER, AND TOTAL MORTALITY AT 10.5 YEARS OF FOLLOW-UP FOR MRFIT PARTICIPANTS

	Number of participants	CHD			Lung cancer			Total mortality		
		Number of deaths	Adjusted RR[a]	95% CI	Number of deaths	Adjusted RR	95% CI	Number of deaths	Adjusted RR	95% CI
Never smoked cigarettes	1,859	44 (2.22)[b]	1.00	—	0 (0.00)	1.00	—	102 (5.15)	1.00	—
Exsmoker	2,813	73 (2.44)			13 (0.43)			163 (5.44)		
Smoker										
1–25	2,572	102 (3.80)	2.18	(1.66, 2.88)	19 (0.71)	3.11	(1.51, 6.41)	211 (7.87)	1.84	(1.52, 2.21)
≥26	5,622	209 (3.58)	2.58	(1.98, 3.35)	87 (1.49)	7.18	(3.76, 13.70)	557 (9.54)	2.70	(2.28, 3.21)
Regression coefficient (SE) for cigarettes/day in proportional hazards model (smoker only)[a]			0.0057 (0.0042)			0.0265 (0.0066)			0.0114 (0.0026)	
P-value			0.52			<0.001			<0.001	

[a] Adjusted for age, serum cholesterol, and diastolic blood pressure.

[b] Rate per 1,000 person-years.

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TABLE 5

RELATIONSHIP BETWEEN SERUM THIOCYANATE AND CHD, LUNG CANCER, AND TOTAL MORTALITY AT 10.5 YEARS OF FOLLOW-UP FOR MRFIT SCREEN 1 SMOKERS

	Number of participants	CHD			Lung cancer			Total mortality		
		Number of deaths	Adjusted RR[a]	95% CI	Number of deaths	Adjusted RR	95% CI	Number of deaths	Adjusted RR	95% CI
Quintile of thiocyanate (μmol/liter)										
<122	1,591	41 (2.45)[b]	1.00	—	15 (0.90)	1.00	—	105 (6.29)	1.00	—
122–156	1,578	63 (3.87)	2.21	(1.63, 2.99)	24 (1.48)	3.05	(1.74, 5.34)	155 (9.53)	2.04	(1.68, 2.47)
157–183	1,555	77 (4.76)	2.82	(2.12, 3.75)	10 (0.62)	1.32	(0.63, 2.75)	147 (9.09)	2.02	(1.66, 2.47)
184–213	1,630	63 (3.74)	2.30	(1.69, 3.13)	29 (1.72)	3.64	(2.11, 6.28)	159 (9.43)	2.13	(1.75, 2.59)
≥214	1,591	59 (3.60)	2.24	(1.64, 3.07)	24 (1.47)	3.34	(1.88, 5.92)	177 (10.81)	2.50	(2.07, 3.03)
Regression coefficient (SE) for thiocyanate in proportional hazards model[a]			*0.0025 (0.0010)*			*0.0037 (0.0017)*			*0.0033 (0.0006)*	
P-value			0.01			0.03			<.001	

[a] Adjusted for age, serum cholesterol, and diastolic blood pressure.
[b] Rate per 1,000 person-years.

TABLE 6

RELATIONSHIP BETWEEN INITIAL AGE OF DAILY CIGARETTE SMOKING AND CHD, LUNG CANCER, AND TOTAL MORTALITY AT 10.5 YEARS OF FOLLOW-UP FOR MRFIT SCREEN 1 SMOKERS

	Number of participants	CHD			Lung cancer			Total mortality		
		Number of deaths	Adjusted RR[a]	95% CI	Number of deaths	Adjusted RR	95% CI	Number of deaths	Adjusted RR[a]	95% CI
Age at screening 35–44										
Age began smoking										
≤15	978	25 (2.42)[b]	1.00	—	3 (0.29)	1.00	—	67 (6.49)	1.00	—
16–17	1,018	31 (2.89)	1.15	(0.67, 1.95)	8 (0.75)	2.81	(0.73, 10.78)	70 (6.52)	0.99	(0.70, 1.38)
18–19	753	16 (2.01)	0.77	(0.41, 1.46)	4 (0.50)	2.04	(0.44, 9.47)	39 (4.90)	0.74	(0.50, 1.11)
20–21	401	14 (3.28)	1.27	(0.66, 2.47)	0 (0.00)	N/A	N/A	20 (4.69)	0.70	(0.42, 1.16)
22–23	167	1 (0.57)	0.21	(0.03, 1.55)	0 (0.00)	N/A	N/A	10 (5.74)	0.85	(0.44, 1.67)
≥24	*185*	*3 (1.52)*	*0.53*	*(0.16, 1.78)*	*0 (0.00)*	*N/A*	*N/A*	*6 (3.04)*	0.45	(0.19, 1.04)
Regression coefficient (SE) for initial age of daily smoking in proportional hazards model[a]			*−0.0277 (0.0305)*			*−0.0602 (0.0798)*			*−0.0381 (0.0204)*	
P-value			0.36			0.45			0.06	
Age at screening 45–57										
Age began smoking										
≤15	1,087	54 (4.86)	1.00	—	22 (1.98)	1.00	—	135 (12.16)	1.00	—
16–17	1,224	51 (4.08)	0.82	(0.56, 1.20)	32 (2.56)	1.36	(0.79, 2.35)	153 (12.23)	1.01	(0.80, 1.27)
18–19	*1,123*	*50 (4.30)*	*0.85*	*(0.56, 1.27)*	*21 (1.80)*	*0.97*	*(0.53, 1.76)*	*114 (9.80)*	*0.80*	*(0.62, 1.02)*
20–21	628	37 (5.76)	1.11	(0.73, 1.69)	7 (1.09)	0.57	(0.24, 1.34)	82 (12.77)	1.02	(0.77, 1.34)
22–23	255	11 (4.55)	0.85	(0.44, 1.63)	6 (2.48)	1.31	(0.53, 3.24)	27 (11.16)	0.89	(0.58, 1.34)
≥24	359	17 (4.60)	0.88	(0.51, 1.53)	3 (0.81)	0.42	(0.13, 1.44)	42 (11.37)	0.90	(0.64, 1.28)
Regression coefficient (SE) *P*-value for initial age of daily smoking in proportional hazards model[a]			*−0.0034 (0.0159)*			*−0.0279 (0.0268)*			*−0.0028 (0.0100)*	
P-value			0.83			0.30			0.79	

[a] Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day.
[b] Rate per 1,000 person-years.

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TABLE 7

RELATIONSHIP BETWEEN CIGARETTE NICOTINE CONTENT AND CHD, LUNG CANCER, AND TOTAL MORTALITY AT 10.5 YEARS OF FOLLOW-UP FOR MRFIT SCREEN 1 SMOKERS

		CHD			Lung cancer			Total mortality		
	Number of participants	Number of deaths	Adjusted RR[a]	95% CI	Number of deaths	Adjusted RR	95% CI	Number of deaths	Adjusted RR	95% CI
Nicotine (mg)										
≤1.0	1,777	68 (3.67)[b]	1.00	—	20 (1.08)	1.00	—	156 (8.42)	1.00	—
1.1–1.4	4,363	160 (3.52)	1.04	(0.80, 1.35)	51 (1.12)	0.97	(0.62, 1.52)	394 (8.68)	1.05	(0.89, 1.24)
≥1.5	1,319	60 (4.41)	1.27	(0.92, 1.77)	24 (1.76)	1.46	(0.85, 2.49)	157 (11.53)	1.36	(1.11, 1.67)
Regression coefficient (SE) for nicotine in proportional hazards model[a]			0.0294 (0.2046)			0.4142 (0.3648)			0.2517 (0.1328)	
P-value			0.89			0.26			0.06	

[a] Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day.
[b] Rate per 1,000 person-years.

TABLE 8

RELATIONSHIP BETWEEN CIGARETTE TAR CONTENT AND CHD, LUNG CANCER, AND TOTAL MORTALITY AT 10.5 YEARS OF FOLLOW-UP FOR MRFIT SCREEN 1 SMOKERS

		CHD			Lung cancer			Total mortality		
	Number of participants	Number of deaths	Adjusted RR[a]	95% CI	Number of deaths	Adjusted RR	95% CI	Number of deaths	Adjusted RR	95% CI
Tar (mg)										
≤15	992	39 (3.77)[b]	1.00	—	12 (1.16)	1.00	—	91 (8.79)	1.00	—
16–19	4,347	160 (3.54)	1.08	(0.80, 1.45)	48 (1.06)	0.81	(0.49, 1.33)	384 (8.49)	1.01	(0.83, 1.22)
≥20	2,120	89 (4.06)	1.19	(0.86, 1.65)	35 (1.60)	1.14	(0.67, 1.94)	232 (10.58)	1.21	(0.98, 1.49)
Regression coefficient (SE) for tar in proportional hazards model[a]			0.0089 (0.0128)			0.0227 (0.0223)			0.0179 (0.0082)	
P-value			0.49			0.31			0.03	

[a] Adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes day.
[b] Rate per 1,000 person-years.

Source: https://www.industrydocuments.ucsf.edu/docs/zlbj0000

Smoking Cessation among Randomized Participants

Smoking cessation in the MRFIT was assessed by self-report validated by the serum SCN level and, later, by expired air carbon monoxide levels (at the 36- and 72-month visits). Quitters were defined as screen 1 smokers, who at the 12-month visit reported not smoking and whose level of serum SCN was below 100 μmol/liter. This definition is consistent with mortality results presented in an earlier report (5).

Both the SI and the UC smokers who stopped smoking during the first 12 months of the trial had lower CHD and total mortality rates than those who continued to smoke (Table 9) (24). There is no evidence of a reduction in lung cancer mortality associated with smoking cessation over this 10-year follow-up period. Most of the lung cancers, however, occurred among the heavier smokers, the group with the lowest cessation rates.

DISCUSSION

The MRFIT results demonstrate that the risk of cancer and CHD mortality is substantially increased among smokers compared with nonsmokers and that this risk increases with the number of cigarettes smoked. These findings are consistent with those from the early longitudinal studies of the 1960s and early 1970s (11).

The MRFIT began in 1972 in a climate of increasing interest in risk factor interventions, including smoking cessation. Of the three clinical trials on the effect of smoking cessation on mortality which have been conducted (5, 25, 26), the

TABLE 9

CHD, LUNG CANCER, AND TOTAL MORTALITY FROM THE END OF THE TRIAL THROUGH 12/31/85 BY CIGARETTE SMOKING STATUS AT 72 AND 12 MONTHS FOR MRFIT SI AND UC SCREEN 1 CIGARETTE SMOKERS

		CHD		Lung cancer		All causes	
	No. men	No. deaths	Rate deaths	No. deaths	Rate deaths	No. deaths	Rate deaths
Special intervention							
Reported smoking cigarettes at 72 months							
Yes	1,810	40	5.91	14	2.07	95	14.03
No	1,734	20	3.04	9	1.37	49	7.45
Reported smoking cigarettes at 12 months							
Yes	564	7	3.28	1	0.47	17	7.96
No	1,170	13	2.93	8	1.80	32	7.21
Usual care							
Reported smoking cigarettes at 72 months							
Yes	2,488	59	6.35	14	1.51	142	15.27
No	1,009	16	4.20	6	1.58	38	9.98
Reported smoking cigarettes at 12 months							
Yes	686	13	5.04	3	1.16	27	10.46
No	323	3	2.44	3	2.44	11	8.96

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MRFIT has been the largest. At the inception of the MRFIT, and throughout its duration, both England and the United States witnessed dramatic declines in the incidence of lung cancer. In the United States, the lung cancer rate per 100,000 white men age 35–44 years dropped from 15.4 in 1970 to 11.2 in 1980 to 9.4 in 1985 (27). Cardiovascular mortality also decreased in the United States (27).

The decline in the incidence of these diseases has been partially attributed to changes in smoking behavior (28). In the United States, two important changes have occurred in the last 30 years: The tar and nicotine content in cigarettes has decreased, and—particularly among the younger age groups—the percentage of individuals who smoke has substantially declined. For example, in 1965, 57.3% of 35-year-old white men smoked cigarettes, but by 1976, the percentage of smokers in this cohort had dropped to 46.8 and by 1985, had dropped further to 36.6 (1).

Although it is difficult to determine how much of the change in lung cancer and cardiovascular mortality in the United States has been due to modification of the cigarette, rather than the decline in the percentage of cigarette smokers, the results of the present study indicate that reduction in the tar and nicotine contents of cigarettes was unlikely to have had an important effect on mortality, since tar and nicotine contents were only weakly related to total mortality. Moreover, the duration of smoking as measured by the age of smoking onset was only weakly related to mortality. However, the duration of exposure to low tar/nicotine cigarettes was unknown. Participants may have switched to these types of cigarettes only after years of smoking higher tar/nicotine products.

The present study suggests that smoking cessation may be related to lower mortality rates from CHD. Individuals who quit smoking during the first year of the trial had a 37.2% lower CHD and 40.9% lower total mortality at 10.5 years than those who were still smoking at the end of one year (24). There was no evidence that smoking cessation resulted in a decrease in lung cancer mortality. This finding is consistent with the results from the large observational study of U.S. Veterans which noted that while risk of lung cancer declined with increasing length of time from initial smoking cessation, substantial excess risk, compared with veterans who never smoked, remained as long as 20 years after quitting smoking (29).

Lung cancer mortality in the MRFIT was more closely linked to dose as measured by the number of cigarettes smoked than was CHD mortality. The heavier smokers were less likely to stop smoking (30, 31). Almost all of the lung cancer deaths continued to occur among men who were heavy cigarette smokers (smoking 25 or more cigarettes per day) in the trial. The relatively low cessation rates among these high risk smokers may partially account for the failure to demonstrate any difference in lung cancer mortality. An irreversible cumulative effect of cigarette smoking exposure similar to radiation and other carcinogens may also be an important factor (28).

The smoking cessation rate for SI men was substantial and somewhat greater than anticipated during the trial (5, 18). However, the cessation rate among UC men was also higher than expected. By 72 months, the cessation rates among screen 1 smokers were 28.1 and 49.3% for UC and SI groups, respectively (30).

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During the first year of the trial, when smoking cessation was the greatest, there was a 15.8% difference in the cessation rate between the SI and UC smokers (30).

The magnitude of the UC cessation rates and the lower than expected UC mortality rate reduced the power of the trial to detect significant differences between SI and UC men in CHD and total mortality. Based on epidemiological data, the 15.8% difference between SI and UC in 12-month cessation rates is estimated to result in a 6% decrease in both CHD and total mortality. After an average of 10.5 years of follow-up, mortality rates among all MRFIT men for CHD and all causes were lower for SI compared with UC men by 10.6 and 7.7%, respectively. Thus, the effects of smoking cessation may have accounted for much of the overall difference in CHD and total mortality between SI and UC participants. These differences due to smoking do not take into account changes in the dose of smoking or any reported smoking cessation after the first 12 months.

CONCLUSION

In summary, the results of the MRFIT are consistent with other studies in demonstrating that compared with men who continue to smoke, men who stop smoking have substantially lower risks of both CHD and total mortality. The key question, therefore, is not whether smoking cessation is beneficial, but rather, whether it is possible to substantially increase the number of individuals who stop smoking and remain exsmokers, especially among the heavier smoking group. The results from this study point to the need for special emphasis on the latter group with regard to smoking cessation in order to reduce its high risk of CHD. This continues to be an important public health concern.

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Association between Baseline Risk Factors, Cigarette Smoking, and CHD Mortality after 10.5 Years[1]

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Methods. The association between baseline risk factors and death from coronary heart disease (CHD) after 10.5 years was investigated for cigarette smokers and nonsmokers who entered the Multiple Risk Factor Intervention Trial (MRFIT).

Results. Rates per thousand person-years of CHD mortality were higher for smokers than for nonsmokers at every level of baseline risk factors examined. There were significant associations between CHD mortality and plasma low-density lipoprotein and high-density lipoprotein cholesterol for smokers and nonsmokers. The inverse association between CHD mortality and high-density lipoprotein cholesterol was significantly stronger among nonsmokers compared with that among smokers and was attributable to a very strong association for former smokers. An inverse relationship between CHD and body mass index was evident for smokers and nonsmokers. Rates of CHD death rose sharply when levels of fasting glucose exceeded 140 mg/dl, and there was a significant association between CHD mortality and blood sugar levels for nonsmokers but not for smokers. For both smokers and nonsmokers, an inverse univariate association between alcohol consumption and CHD mortality was evident. This association, however, did not persist after adjustment for plasma high-density lipoprotein cholesterol.

Conclusion. Intervention on blood pressure and blood lipids is particularly important among cigarette smokers because of their increased risk of CHD death. The different associations between high-density lipoprotein cholesterol, fasting serum glucose, and CHD mortality for smokers and nonsmokers requires further investigation.

INTRODUCTION

The 12,866 participants randomized to the Multiple Risk Factor Intervention Trial (MRFIT) have been followed for an average of 10.5 years. Extensive information regarding risk factors for coronary heart disease (CHD) was collected from all participants upon entry into the trial. A previous report evaluated the association between baseline risk factors and mortality from CHD and all causes during the first 7 years of follow-up (1). This report found that levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), blood pressure (BP), and cigarette smoking were strong predictors of CHD mortality. Cigarette smoking was also a strong predictor of all-cause mortality.

After 10.5 years, randomized MRFIT cigarette smokers were at increased risk of death from CHD, lung cancer, and all causes compared with nonsmokers (2).

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Cigarette Smoking and Lung Cancer Cell Types

Alfredo Morabia, MD, PhD,*† and Ernst L. Wynder, MD*

The role of tobacco smoke in the development of lung cancer is well known for squamous and small cell types, somewhat less so for adenocarcinoma, and not specifically assessed for large cell carcinoma. In the current analysis, based on 851 men and 507 women with lung cancer and their matched controls (888 men and 608 women), smoking was associated with each lung cancer cell type, and differences in smoking habits by cell types were small. However, the increase of lung cancer risk according to number of cigarettes per day was stronger for small cell and oat cell carcinoma than for adenocarcinoma. There was no increase for large cell carcinoma. For squamous cell carcinoma, this dose response was weak among men and strong among women. The strength of the association between smoking and lung cancer cell types may be related to cancer location, with more peripheral lung cancer types (such as adenocarcinoma and large cell carcinoma) showing weaker associations than more central tumors (such as squamous or small cell and oat cell carcinoma). *Cancer* 68:2074–2078, 1991.

A TRANSITION is taking place in the epidemiology of lung cancer. In the United States, the overall mortality of lung cancer will start declining in the 1990s for men and after the year 2000 for women as a result of lower rates observed among men and women younger than 45 years of age.[1] However, the proportion of adenocarcinomas and the proportion of women with lung cancer are rising. This evolution may be a result of changes in types of cigarettes smoked and the additional influence of non-tobacco-related factors, such as occupational, hormonal, or dietary factors.[2–4]

The role of tobacco smoke in the development of lung cancer is well known for squamous and small cell types, somewhat less so for adenocarcinoma, and not specifically assessed for large cell carcinoma. In Kreyberg's[5,6] theory, adenocarcinoma and bronchioloalveolar carcinoma were not tobacco related. This theory received empiric support from studies based on small numbers of adenocarcinoma cases.[7–9] However, most studies report a greater risk of adenocarcinoma among smokers than nonsmokers, the dose–response gradient being either similar[2,10–12] or weaker than that for squamous or small cell or oat cell carcinoma.[13–16] Because previous studies on smoking and cancer of the lung rarely contained detailed information on cell types and often lacked a formal control group, we conducted a case-control study to determine whether the effect of tobacco smoke on lung cancer differed by cell type.

Materials and Methods

We studied 851 men and 507 women with lung cancer and their matched controls (888 men and 608 women) after exclusion of six men and 13 women with with mixed cell or nondifferentiated cell lung cancer. All patients were interviewed between 1985 and May 1990 in nine hospitals in New York, Michigan, and Pennsylvania as part of the American Health Foundation case-control study of tobacco-related diseases.

The design of this study was described elsewhere.[17] Briefly, in the participating hospitals, we try to interview all incident cases of tobacco-related cancers (lung, upper respiratory and upper digestive tracts, kidney, bladder, liver, and pancreas) or myocardial infarction. For each case, we interview at least one control matched to the case by age (± 5 years), hospital, and date of admission (± 2 months). During the hospital stay, trained interviewers collect detailed information on smoking from all study participants and abstract lung cancer cell types from pathology reports.

We separated the cell types into squamous and epidermoid, small cell and oat cell, large cell, and adenocarci-

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noma. We excluded bronchioloalveolar carcinoma (BAC) because of the small number of cases. In Figure 1, the proportion of never smoked among BAC patients was taken from a manuscript in preparation that analyzed all cases of BAC recruited to the American Health Foundation Study between 1977 and May 1990.

We assessed the exposure to tobacco smoke as the current number of cigarettes per day, cumulated number of cigarettes ever smoked, cumulated years of smoking, and average number of cigarettes per day. Intensity-related factors were coded as follows: inhale deeply *versus* moderately, slightly, or not at all; have first cigarette within 15 minutes after awakening *versus* more than 15 minutes; smoke only filter cigarettes *versus* nonfilter or mixed; smoke the whole cigarette *versus* less than 75% of it.

We adjusted multivariate odds ratios for age at diagnosis, race, and hospital of admission, *i.e.*, the matching factors, and used analysis of variance to compute adjusted means or proportions and to test for heterogeneity between means. Adjusted relative odds and their confidence intervals were computed using logistic regression. The analyses were done with standard statistical software.[18]

Results

Compared with controls, male patients were less often Jewish and a larger proportion of all male and female patients had less than 13 years of education (Tables 1 and 2). For both sexes small cell and oat cell and adenocarcinoma appeared in a larger proportion of blacks.

The adjusted proportion of never smoked increased progressively in both men and women from small cell and oat cell, to squamous cell, large cell, adenocarcinoma, and BAC (Fig. 1). The trend was clearer in women. The controls had a larger proportion of never smoked than any of the cell types. In each category, women more often never smoked than men.

We compared adjusted means of smoking-related variables, first including the four cell types and the controls and then excluding controls. For the analyses of current smokers including controls (Tables 3 and 4), we found statistically significant differences for all variables for both men and women, except for smoking only filter cigarettes among women. However, after excluding controls from these analyses, an analysis of variance F test remained statistically significant for only three variables among men (Table 3): (1) the cumulated years of smoking were somewhat lower (40.1 years) and (2) the age when started smoking slightly older (17.5 years) for small cell and oat cell cases compared with the other cell types; and (3) the average number of cigarettes per day was slightly lower for adenocarcinoma (27.4). In contrast, there was no difference by cell type of depth of inhalation, timing of the first cigarette of the day, proportion of the cigarette smoked, or choice of filter cigarettes. Also, smoking-related characteristics did not differ by cell type among current smokers who were women, but the statistical power was low because of small sample sizes (Table 4).

Among both male and female ex-smokers (not shown

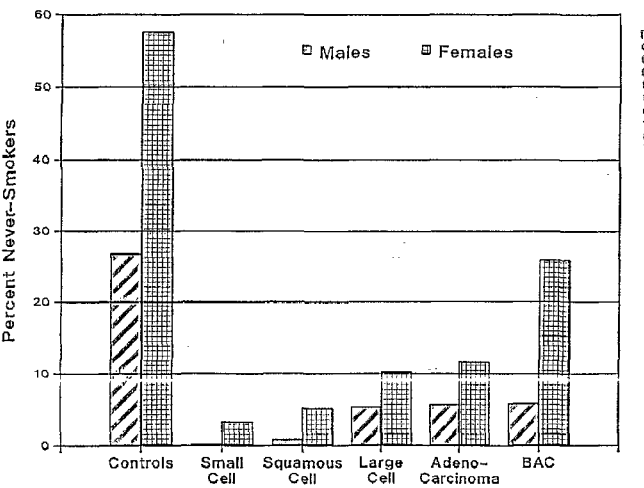

FIG. 1. Proportion of never smoked by sex and cell types, adjusted for age at diagnosis, race, and state. The sample sizes for controls, small/oat cell, squamous cell, large cell, adenocarcinoma, and bronchioloalveolar carcinoma (BAC) are, for men, 888, 111, 305, 97, 338, and 61, respectively, and for women, 608, 73, 117, 59, 258, and 48, respectively.

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TABLE 1. Selected Demographic Characteristics of Male Lung Cancers and Controls by Cell Types: US Hospital Patients, 1985–1990

	Lung cancer cell types									
	Squamous		Small/oat		Large		Adenocarcinoma		Controls	
Men	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Married	244	80.0	84	75.7	83	85.6	284	84.0	736	82.9
Black	32	10.5	16	14.4	9	9.3	50	14.8	95	10.7
Protestant	92	30.2	42	37.8	30	30.9	110	32.5	270	30.4
Catholic	171	56.1	55	50.0	50	51.6	178	52.7	416	46.9
Jewish	35	11.5	9	8.1	14	14.4	44	13.0	181	20.4
Years of education										
≤ 11	80	26.2	23	20.7	28	28.9	94	27.8	158	17.8
12	108	35.4	42	37.8	28	28.9	82	24.3	228	25.7
13–15	47	15.4	22	19.8	15	15.5	74	21.9	173	19.5
16+	70	23.0	24	21.6	26	26.8	88	26.0	329	37.1

in table), all cell types started smoking at a similar age (approximately 17 years for men and 18 years for women), but small cell and oat cell cases stopped smoking at an older age (men, 53 years; women, 54 years) and were more exposed to tobacco smoke with respect to duration (35.4 years) and absolute amount (437,000 cigarettes) compared with the three other cell types. Male ex-smokers with small cell and oat cell carcinoma reported smoking their first cigarette of the day within 15 minutes after awakening more frequently (72%) than patients with other cell types. Female ex-smokers with adenocarcinoma had smoked filter cigarettes on average for a shorter period (17 years) than patients with other cell types.

Table 5 includes only those who ever smoked. For all cell types except large cell, the relative odds of lung cancer increased with an increasing number of cigarettes per day; the relative odds and the trend were stronger among current smokers than ex-smokers. In men, the dose response was strong for small cell and oat cell carcinoma, less so for squamous cell and adenocarcinoma, and absent for large cell carcinoma. In women, the dose response was strong for squamous and small cell and oat cell, less so for adenocarcinoma, and not linear for large cell.

Discussion

We found, as expected, that lung cancer cases smoke more than controls, regardless of the cell type of the carcinoma. This is illustrated by the strikingly smaller proportion of never smoked among cases of any type than among controls (Fig. 1). We also discovered that, on average, differences in smoking behavior between cell types were small and not systematic in amount (cumulated years of cigarette smoking, cumulative number of cigarette, and lifetime average number of cigarettes per day) or intensity (depth of inhalation, timing of the first morning cigarette, and choice of filter cigarette). In a Western European case-control study, it also was found that intensity-related measures of smoking did not differ systematically by cell type.[14] Nonetheless, we noticed that the gradient in lung cancer risk was related to the number of cigarettes per day and differed by cell types. The linear dose response

TABLE 2. Selected Demographic Characteristics of Female Lung Cancers and Controls by Cell Types: US Hospital Patients, 1985–1990

	Lung cancer cell types									
	Squamous		Small/oat		Large		Adenocarcinoma		Controls	
Women	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Married	74	63.2	38	52.1	30	50.9	155	60.1	382	62.8
Black	7	6.0	8	11.0	5	8.5	33	12.8	50	8.2
Protestant	41	35.0	22	30.1	20	33.9	72	27.9	176	29.0
Catholic	57	48.7	44	60.3	26	44.1	127	49.2	292	48.0
Jewish	18	15.3	7	9.6	12	20.3	57	22.1	128	21.1
Years of education										
≤ 11	19	16.2	23	31.5	12	20.3	45	17.4	105	17.3
12	62	53.0	27	37.0	23	39.0	127	49.2	247	40.6
13–15	16	13.7	12	16.4	11	18.6	47	18.2	129	21.2
16+	20	17.1	11	15.1	13	22.0	39	15.1	127	20.9

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TABLE 3. Adjusted Averages* of Smoking-Related Characteristics Among Current Cigarette Smokers by Lung Cancer Cell Types: US Male Hospital Patients, 1985–1990

Characteristic among men	Lung cancer cell types					*F* test	
	Squamous (n = 157)	Small/oat (n = 68)	Large (n = 51)	Adenocarcinoma (n = 170)	Controls (n = 220)	Overall	Between cell types
Cumulated years of smoking	42.7	40.1	42.1	42.1	39.5	8.9†	3.4‡
Cumulative number of cigarettes (×1000)	477	450	475	424	347	12.2†	2.2
Average number of cigarettes/day	31.2	30.7	31.4	27.4	23.5	11.3†	2.8‡
Age start smoking	16.0	17.5	15.4	16.6	18.0	7.2†	3.9†
Inhale deeply (%)	45.9	38.9	38.7	40.5	28.8	3.24‡	0.6
First cigarette 15 minutes or less after wake up (%)	63.6	56.3	65.0	54.2	44.4	4.2†	1.4
Only filter cigarettes (%)	7.4	14.1	6.8	13.0	16.7	2.5‡	1.6

* Adjusted for age at diagnosis, state, and race.
† $P < 0.01$.
‡ $P < 0.05$.

was strong for small cell and oat cell carcinoma, less strong for adenocarcinoma, and absent for large cell carcinoma in both sexes. For squamous cell carcinoma, this dose response was stronger in women than in men.

The weaker dose response for adenocarcinoma compared with squamous or small cell or oat cell carcinoma was consistent with other reported findings.[13,15] The relative odds of adenocarcinoma reported by others[15] were 1.0 (0 to 18 pack-years), 1.3 (18 to 56 pack-years), and 1.5 (> 56 pack-years). The relative odds of adenocarcinoma with years of smoking were, in another study,[15] 1.0 (< 30 years), 0.7 (31 to 40 years), 1.9 (41 to 50 years), and 1.4 (≥ 51 years). Using light smokers (one to nine cigarettes per day) as a reference group, others found a clear gradient for adenocarcinoma with the number of cigarettes per day in men but not in women.[14] Failure to observe a dose response with smoking for large cell carcinoma in both sexes was puzzling, but consistent with reported findings.[9,10] The latter group[10] found the same incidence of lung cancer among smokers of ten to 19 and 20+ cigarettes per day in their 10-year follow-up study.

Thus, despite comparable smoking habits, the strength of association with tobacco smoke seemed to differ by cell type. The explanation of this may lie in the lower exposure to tobacco smoke particles to sites that are more peripheral in the respiratory tract. Squamous and small cell and oat cell carcinoma occur mainly in large central bronchi; adenocarcinoma chiefly are located peripherally; and large cell carcinoma tend to be peripheral and subpleural.[12,19] Others also stressed the importance of anatomy in the genesis of lung cancer.[20]

However, in addition to the small number of large cell carcinoma cases in our study, pathologic diagnosis of this cell type is not accurate. According to Yesner,[21] large cell carcinoma is a transitional stage between small cell and adenocarcinoma or squamous cell carcinoma. It is a diagnosis of exclusion applied to a tumor with atypical histologic findings that is often impossible to distinguish from poorly differentiated small cell or oat cell, squamous cell, or adenocarcinoma if the tissue fragments are small.[19] Large cell carcinoma is, therefore, a wastebasket category.[12] Others found that interobserver agreement was

TABLE 4. Adjusted Averages* of Smoking-Related Characteristics Among Current Cigarette Smokers by Lung Cancer Cell Types: US Female Hospital Patients, 1985–1990

Characteristic among women	Lung cancer cell types					*F* test	
	Squamous (n = 75)	Small/oat (n = 50)	Large (n = 40)	Adenocarcinoma (n = 165)	Controls (n = 150)	Overall	Between cell types
Cumulated years of smoking	39.8	40.8	39.9	40.2	35.8	11.4†	0.5
Cumulative number of cigarettes (×1000)	343	377	327	350	260	7.8†	0.9
Average number of cigarettes/day	24.1	25.5	22.3	23.6	18.8	6.4†	0.8
Age start smoking	19.1	18.4	18.6	18.4	21.5	8.2†	0.5
Inhale deeply (%)	28.2	36.4	25.2	31.0	16.3	2.8‡	0.5
First cigarette 15 minutes or less after wake up (%)	57.3	55.2	53.0	53.9	31.5	5.3†	0.1
Only filter cigarettes (%)	29.1	22.9	26.7	27.9	38.3	1.9	0.4

* Adjusted for age at diagnosis, state, and race.
† $P < 0.01$.
‡ $P < 0.05$.

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TABLE 5. Adjusted* Relative Odds of Lung Cancer with Cigarette Smoking by Sex and Cell Types: US Hospital Patients, 1985–1990

			Lung cancer cell types							
			Squamous		Small/oat		Large		Adenocarcinoma	
Sex	Smoking status	No. of cigarettes/day	Cases	RO (95% CI)	Cases	RO (95% CI)	Cases	RO (95% CI)	Cases	RO (95% CI)
Male	Current smoker	1–19	18	1.0 (referent)	3	1.0 (referent)	9	1.0 (referent)	23	1.0 (referent)
		20–29	39	1.6 (0.9–2.9)	25	6.0 (1.7–20.4)	13	1.1 (0.5–2.7)	48	1.7 (1.0–3.1)
		30+	100	2.3 (1.3–3.9)	40	5.5 (1.6–18.2)	29	1.0 (0.5–2.3)	99	1.9 (1.1–3.2)
	Quit	1–19	16	0.6 (0.3–1.2)	5	1.3 (0.3–5.6)	5	0.4 (0.1–1.3)	19	0.6 (0.3–1.2)
		20+	127	1.4 (0.8–2.4)	36	2.6 (0.8–8.8)	36	0.8 (0.4–1.7)	127	1.3 (0.8–2.1)
Female	Current smoker	1–19	10	1.0 (referent)	6	1.0 (referent)	6	1.0 (referent)	31	1.0 (referent)
		20–29	21	1.5 (0.7–3.3)	16	1.8 (0.7–4.9)	17	1.9 (0.7–4.9)	66	1.3 (0.8–2.2)
		30+	42	2.7 (1.3–5.7)	28	3.2 (1.2–8.1)	17	1.4 (0.5–3.8)	66	1.5 (0.9–2.6)
	Quit	1–19	4	0.4 (0.1–1.2)	3	0.5 (0.1–2.0)	5	0.9 (0.3–3.1)	21	0.7 (0.4–1.3)
		20+	35	2.0 (1.0–4.3)	18	1.8 (0.7–4.9)	9	0.8 (0.3–2.4)	49	0.9 (0.5–1.5)

RO: relative odds; CI: confidence interval.

* Adjusted simultaneously for age, race, and state.

more than 75% for small cell or oat cell, squamous, or adenocarcinoma but only 40% for large cell carcinoma.[22] The absence of dose response may be a result of overdiagnosis of large cell type in the one to 19 cigarettes-per-day smokers or to underdiagnosis of large cells in heavier smokers, especially among men. Thus, although plausible, our findings need to be replicated by other researchers.

Although our data do not show that patients with adenocarcinoma smoke filtered cigarettes more frequently than do those with other cell types, the increasing prevalence of adenocarcinoma reported[2–4] may still be related to the overall tendency of smokers to prefer filtered cigarettes.[23] Smokers of filtered cigarettes inhale smaller particles that reach deeper airways and may be influencing the genesis of more peripheral tumors.[20,24] Besides occupational exposures, hormonal factors, adiposity, and dietary factors also may be responsible for this epidemiologic transition.[25] The latter factors have received too little attention in the literature.

In conclusion, the strength of the association between smoking and lung cancer cell types seems to be related to tumor location. More peripheral cancer types, such as adenocarcinoma and large cell carcinoma, show weaker associations than more central tumors, such as squamous or small cell or oat cell carcinoma.

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Type of tobacco and risk of lung cancer: a case-control study from Uruguay

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Summary

During the time period January 1988-December 1989, a case-control study involving 224 cases of lung cancer and 252 controls was carried out at the Instituto de Oncologia, Montevideo, Uruguay, in order to analyze the patterns of risk of lung cancer, associated with smoking blond (flue-cured) and black (air-cured) cigarettes. Mixed smokers carried a significantly higher RR of 3.2, when compared with smokers of blond cigarettes. Lifetime smokers of black cigarettes displayed a non-significant 30% increased risk compared with blond cigarette smokers. Since the differences between mixed and pure black were not significant, and the confidence bounds between both categories were overlapping, the possibility of a chance finding arises. If mixed and lifelong (pure) black tobacco smoking is in fact not different, then ever use of black tobacco is the relevant measure. Ever use of black tobacco was associated with a significant 2-fold increase in the relative risk for all cases and for squamous cell lung cancer. Given the high prevalence of ever use of black tobacco in Uruguay, the attributable fraction for black tobacco smoking in lung cancer could be as high as 29.3 percent.

Introduction

Lung cancer is the leading neoplastic cause of death among Uruguayan males, with an age-adjusted mortality rate of 56.8 for the whole country and an age-adjusted incidence rate

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of 83.3 for 1987 in the capital city of Montevideo [1]. Numerous prospective and retrospective epidemiological studies have confirmed that cigarette smoking is the major cause of lung cancer. Furthermore, the risk of lung cancer increases with all types of tobacco products [2].

Uruguay is characterized by a high proportion of smokers of black tobacco cigarettes. In fact, about 40% of the male population smokes black products. This habit has been consistently shown as a risk factor for esophageal, oropharyngeal, laryngeal and bladder cancers [3–10]. According to chemical analysis, black tobacco contains lower amounts of polycyclic hydrocarbons and higher amounts of *N*-nitroso compounds than blond tobacco [11]. In two previous studies on lung cancer, black tobacco smokers showed an increase in risk of 70%, taking as referents smokers of blond tobacco [12, 13]. Both studies were handicapped by the low proportion of smokers of blond tobacco; in this sense Uruguay appears to be a rather convenient place to address the point, due to the similar proportion of smokers of both kinds of cigarettes. The objective of the present study is to estimate the risk associated with smoking different types of tobacco.

Subjects and Methods

During the time period January 1988 to December 1989, all incident cases of lung cancer admitted for diagnosis and/or treatment to the Cancer Institute of Montevideo, Uruguay, were selected for this study. In total, there were 235 cases occurring in men and 17 in women. The study was restricted to males because of the small number of females. Nine cases were unable to complete the questionnaire, due to advanced disease. One further case was excluded due to a diagnosis of rhabdomyosarcoma. Since the study was designed in order to estimate the risk of the type of tobacco, the only non smoker case was excluded from the study, leading to a final total of 224 cases. Of these cases, 197 had histologic diagnosis of lung carcinoma. Squamous cell carcinomas comprised the largest group (98 cases), followed by adenocarcinoma (41 cases) and small cell cancers (33 cases). Twenty-seven cases with clinical, radiologic and endoscopic evidence of lung cancer were also included in the analysis. In the same period, 793 male patients afflicted with other cancers or non-neoplastic conditions, were also admitted to the Institute of Oncology. From this potential source of controls, 86 were excluded due to terminal illness, 366 due to a diagnosis of tobacco-related cancer, 43 with uncertain primary site, and 46 non-smokers. As a final result, 252 patients with a variety of disorders were used as controls. Both cases and controls were interviewed by 3 trained social workers, unaware of the hypothesis to be tested and of any previous exposure. The questionnaire included, among other variables, information concerning demographic variables, social class, occupation, and a complete tobacco history, and was administered to all patients shortly after admission.

The type of tobacco smoked was classified as blond or black, according to the commercial brands registered in all questionnaires. The category 'mixed' was used to designate those smokers which used both blond and black tobacco, either synchronically or metachronically. In a later stage of the analysis, lifelong (pure) blond tobacco smokers were compared with ever smokers of black tobacco (mixed plus pure black).

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TABLE 1
Distribution of cases by histologic type

Type	Frequency	Percent
Squamous cell	98	43.8
Small cell	33	14.7
Adenocarcinoma	41	18.3
Large cell	11	4.9
Unclassified	14	6.2
Clinical diagnosis	27	12.1
Total	224	100.0

Data analysis

Univariate estimates of relative risk, approximated by the odds ratio, were obtained by exponentiating the coefficient of each variable. Since the study followed an unmatched design, unconditional logistic regression was used in order to obtain multivariate estimates for each study variable. Different models were fitted, using the adjusting variables as categorical or continuous. The final models included categorical variables. All estimations were performed using the program GLIM [14].

Results

In Table 1, the distribution of cases by histologic type is shown. In accordance with most series of western countries, squamous cell carcinoma was the most frequent type (43.8%), followed by small cell carcinoma and adenocarcinoma.

TABLE 2
Distribution of controls by diagnosis

ICD-9	Site	*N*	%
173	Skin cancer	70	27.8
185	Prostatic cancer	38	15.1
200-8	Lymphoma-leukemia	29	11.5
153-4	Colorectal cancer	29	11.5
–[a]	Non-neoplastic diseases	27	10.7
–[b]	Other malignant tumors	16	6.2
187	Cancer of the penis	12	4.8
151	Gastric cancer	12	4.8
186	Cancer of the testis	6	2.4
171	Sarcomas	6	2.4
191	Central nervous system	5	2.0
210-4	Benign tumors	2	0.8
–	Total	252	100.0

[a]Diseases of the eye, hernia, osteoarticular disorder.
[b]Melanoma, parotid, gallbladder, and thyroid cancer.

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TABLE 3
Distribution of cases and controls by sociodemographic factors

Variable	Cases		Controls	
	No.	%	No.	%
Age (years)				
≤ 54	57	25.5	63	25.0
55–64	69	30.8	58	23.0
65–74	65	29.0	78	31.0
75+	33	14.7	53	21.0
County				
Montevideo	102	45.5	106	42.1
Other	122	54.5	146	57.9
Residence				
Urban	156	69.6	178	70.6
Rural	68	30.4	74	29.4
Education (years)				
0–3	64	28.6	83	32.9
4+	160	71.4	169	67.1
Monthly income (dollars)				
≤63	155	69.2	170	67.5
64+	69	30.8	82	32.5
No. of patients	224		252	

In Table 2, the distribution of controls by ICD-9 rubric is shown. Only 27 patients (10.7%) were afflicted by non-neoplastic diseases. Among the cancer sites, skin cancer was the most frequent, followed by prostatic cancer, leukemias and lymphomas.

TABLE 4
Relative risks of lung cancer for intensity, cessation, and duration of smoking

Variable	Category	Cases/controls	RR	95% CL
Amount[a] (cig/day)	1–10	21/78	1.0	–
	11–20	61/89	2.0	1.1–3.7
	21–30	53/35	4.2	2.1–8.5
	31+	89/50	5.1	2.7–9.7
Chi-squared= 32.7		$P<0.001$		
Duration[b] (years)	1–29	28/78	1.0	–
	30–39	34/46	1.9	0.9–4.0
	40–49	70/48	5.6	2.7–11.5
	50+	92/80	7.1	3.1–16.2
Chi-squared= 29.2		$P<0.001$		
Years since quit[b]	Current smokers	177/144	1.0	–
	1–4	21/18	1.0	0.5–2.0
	5–9	14/15	0.9	0.4–2.2
	10+	12/75	0.1	0.0–0.2
Chi-squared= 43.3		$P<0.001$		

[a]Adjusted for age, county, education, income, smoking duration, filter use and type of tobacco.
[b]Adjusted for age, county, education, income, amount smoked, filter use and type of tobacco.

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TABLE 5
Relative risks of lung cancer for type of tobacco and other smoking variables

Variable	Category	Cases/controls	RR	95% CL
Type of tobacco[a]	Pure blond	56/112	1.0	–
	Mixed	71/50	2.8	1.6–4.9
	Pure black	97/90	1.3	0.8–2.3
Chi-squared= 1.3		P=0.25		
Type of tobacco[a]	Pure blond	56/112	1.0	–
	Ever black	168/140	1.9	1.2–2.9
Filter use[b]	No	156/150	1.0	–
	Yes	68/102	0.4	0.2–0.7
Hand rolling[a]	No	40/79	1.0	–
	Yes	184/173	1.6	0.9–2.9

[a]Adjusted for age, county, urban/rural condition, education, income, smoking duration, smoking amount, cessation, and filter use.
[b]Adjusted for age, county, education, income, smoking duration, amount and type of tobacco.

Aside that controls were slightly older than cases, the distribution by residence, urban/rural condition, education and income was very similar for both cases and controls (Table 3). Intensity of smoking, measured in lifetime average consumption of cigarettes per day, showed a strong dose-response pattern with a RR of 5.1 for heavy smokers (Table 4). Also, smoking duration displayed a monotonic gradient of increasing risks, with a highly significant test for linear trend. Interestingly, smoking cessation was associated with a reduction in risk of 90% after 10 years since stopping, but showed a sustained risk before this time.

In Table 5, the effect of the type of tobacco smoked is shown, taking as the referent category smokers of blond tobacco. The highest risk was carried by mixed smokers (RR=2.8). Concerning pure black tobacco smokers, there was a 30% increase in risk, which was non significant. Ever smokers of black tobacco showed a significant increase in risk of 1.9, compared with lifelong smokers of blond tobacco. The use of filter cigarettes was associated with a significant reduction in risk of 60%, and smokers of hand-rolled cigarettes showed an RR of 1.6. The effect of the type of tobacco was further explored by histologic type of lung cancer (Table 6).

TABLE 6
Relative risks of lung cancer for ever smokers of black tobacco. Referent category: lifetime smokers of blond tobacco[a]

Cell type	No. cases	RR	95% CL
Squamous cell	98	2.75	1.46–5.18
Small cell	33	2.03	0.67–6.08
Adenocarcinoma	41	1.75	0.76–4.07
Other types	25	2.73	0.82–9.12
No morphology	27	1.05	0.37–2.94
All cases	224	1.88	1.18–2.99
All cases with histology	197	2.12	1.29–3.46

[a]Adjusted for age, residence, urban/rural condition, education, income, amount smoked, smoking duration, years since quit, and filter use.

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Ever smokers of black tobacco showed increased relative risks for squamous cell, small cell and large cell carcinomas. Adenocarcinoma displayed a moderate increase in risk, whereas cases without histologic verification displayed no effect of black tobacco.

Discussion

The present study replicates the previous findings concerning main tobacco variables, like smoking amount and duration [15, 16]. Regarding the type of tobacco, mixed smokers showed the highest risk, whereas smokers of black tobacco displayed a slightly elevated relative risk of 1.3. This pattern of risks for different types of toabcco smoking, showing a greater effect for mixed smokers could have resulted from bias or a chance finding. Concerning bias, the similar distribution of cases and controls according to socio-demographic variables makes unlikely the existence of selection bias. It is conceivable that patients afflicted by lung cancer might be more concerned about their past smoking habits, giving therefore a more precise response to the questionnaire. This could have resulted in a higher proportion of mixed smokers among cases. Although this possibility cannot be excluded, the fact that almost 90% of the controls were cancer controls, suggests a similar recall [17]. In order to exclude interviewer bias, we performed separate analysis for each interviewer, and the results were very similar. The possibility of residual confounding is an unlikely explanation for the high risk associated with smoking both types of tobacco, since this variable was fully controlled for age, residence, education, income, amount smoked, duration, years since quit, and filter use. Since our study examined only tobacco variables, it is not possible to exclude confounding due to other risk factors for lung cancer like occupation and diet. Nevertheless, the strength of the association makes this possibility unlikely.

In order to exclude a chance finding, we also recalculated the relative risk of mixed smokers taking as referents black tobacco smokers. This resulted in a non-significant increase of the relative risk for mixed smokers, with overlapping confidence bounds (RR=1.84 CI=0.97–3.49). Thus, this estimation supports the possibility of a chance finding. On the other hand, the existence of a real effect for mixed smokers cannot be excluded. A recent study on oesophageal cancer, conducted in Thailand, showed a relative risk 1.7 times higher for mixed smokers, compared with pure black tobacco smokers (F.X. Bosch, personal communication). If the difference between mixed and black tobacco smokers is merely due to random variation, then ever smoking black tobacco is the relevant measure, and the significant increase in risk associated with this more crude measure of black products use, could have important epidemiologic implications. Assuming that almost 45% of the Uruguayan population ever smoked air-cured cigarettes, the crude attributable risk could be as high as 29.3%. Of course, this finding needs further elaboration and replication from forthcoming studies. Concerning the mechanisms of action, a more powerful role of black tobacco in early stages of carcinogenesis has been suggested [10]. This could be related with the higher levels of tobacco-specific *N*-nitroso compounds with organ-specific lung activity in black tobacco.

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Acknowledgement

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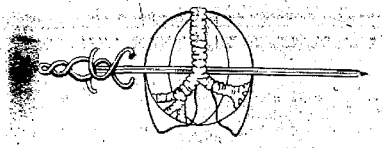

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019

PREDICTIVE VALUE OF CURRENT CIGARETTE SMOKING, PACK YEARS AND TAR EXPOSURE IN THE ESTIMATION OF LUNG CANCER RISK. J Virtamo[1], PR Taylor[2], JK Huttunen[1], BK Edwards[2], P Järvinen[1], J Haapakoski[1], A Hartman[2], J Haukka[1], OP Heinonen[1], D Albanes[2] and P Greenwald[2].
[1]National Public Health Institute, Helsinki, Finland and [2]National Cancer Institute, Bethesda, Maryland, USA.

Now that the use of 'light' cigarettes is well-established, is there predictive value in including tar exposures in lung cancer risk estimations?

Over 29,000 smoking men aged 50-69 years were recruited in the ATBC Study, a double-blind, placebo-controlled trial aimed at preventing lung cancer with alpha-tocopherol and beta-carotene. Smoking was recorded at baseline. 475 men have had lung cancer in 3-6 years of follow-up.

The risk increased 1.8-fold (relative risk, RR = 1.8) with the number of daily cigarettes, from 14 or less to 30 or more. Daily tar exposure from cigarettes had a similar association. Pack years had a positive linear association with lung cancer risk; RR was 4.0 in the highest quintile compared to the lowest (the incidence of lung cancer in quintiles was 29, 22, 15, 12 and 7 per 1000, respectively). The lifetime tar exposure based on the tar content of the current brand was not superior to pack years in predicting lung cancer; RR was 3.6 in the highest quintile compared to the lowest. Thus taking into account the tar content of the current brand does not improve the estimation of lung cancer risk compared to the conventional smoking information.

020

HE XINGZHOU, CHEN HONG, CHEN WEI, R.S. CHAPMAN
INSTITUTE OF ENVIRONMENTAL HEALTH & ENGINEERING, BEIJING, CHINA

A case-control study on risk factors of lung cancer in no-smoking woman in rural area, China

In Xuanwei County, Yunnan Province, the lung cancer mortality among females is the highest in China, and tobacco smoking rate is below 0.2%. The former studies have shown a strong association of lung cancer mortality with indoor air pollution from "smoky" coal combustion and shown an obvious on-site exposure-response relationship between lung cancer mortality and benzo[a]pyrene concentration in indoor air.

A case-control study involving interviews with 139 females lung cancer patients and 139 population based controls was conducted in 1989. The risks of lung cancer were higher among the women reporting local "smoky" coal use in their home. Hormonal factors were suggested by an increased risk associated with late menopause and with shorter menstrual cycle length. Factors such as history of chronic bronchitis and family hisyory of lung cancer counld increase the risks of contracting lung cancer, but no positive association of lung cancer and passive smoking was found in this study.

021

THE PROBLEM OF THE FUTURE. THE DISCREPANCY BETWEEN NUMBERS OF NEW CANCERS TOTALLY, LUNG CANCER ESPECIALLY AND THE SOCIETY AS A WHOLE IN YEAR 2010.
S.HAGEN, ULLEVAL HOSPITAL, OSLO, NORWAY.

Norway with a stable uniform population, a Cancer Register which for years have picked up all new cancers and a Bureau of Statistics keeping an eye on everyone, will be used to demonstrate what we all at least in the western world, as soon as possible, should be aware of about the coming 20 years and take precautions if possible. The population as a whole will increase slowly, in year 2010 around + 8%. The agegroup 20-39 years will be reduced by around 8%. Those 80 years and older and especially those 85+ years increase dramatically. The implications of these predictible changes in the population have huge concequenses for the numbers of cancer patients, totally 50% increase. The babyboom from the fifties, those 40-69 years, will really be hit giving that agegroup 70% more cancers. In numbers this means for each 10 new cancers in 1990 you will have 7 more in 2010. Of those age 80+ the increase is 79% related to 1990. Lungcancer alone shows already at year 2000 a 50% increase for the whole population.

CONCLUTION:
In 2010 the population has increased with around 8%, new cancers with 50%, 70% among those 40-69 years. For lung cancer there is a 50% increases early as in year 2000. Those recruting around the clock care-service, those 20-39 years, have decreased by 8%.

022

The occupational distribution of mortality of lung cancer in Shijiazhuang

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Cancer Institute Hebei, Hospital of Hebei Provence*

The mortality of lung cancer in the population of 2,423,057 was analysed in Shijiazhuang from 1974 to 1976. Among the male population, the mortality in worker peasent, citizen and country employee was $32.66/10^6$ (relative risk=2.36), $4.57/10^6$ (RR=0.33), $0.28/10^6$ (RR=0.02) and $21.73/10^6$ (RR=1.57), respectively. Among the female, the mortality in country employee, peasent, citizen and worker was $14.51/10^6$ (RR=1.39), $5.32/10^6$ (RR=0.51), $4.07/10^6$ (RR=0.39) and $3.76/10^6$ (RR=0.36), respectively. During the man worker group, the mortality of commerical employee was $30.72/10^6$ (RR=2.22) and the highest, and of the other people going in for mine, traffic or postal, textile and chemical was $5.81/10^6$ (RR=0.42), $2.21/10^6$ (RR=0.16), $0.55/10^6$ (RR=0.04) and $3.32/10^6$ (RR=0.24), respectively. The highest mortality of the chemical was $6.47/10^6$ (RR=0.62) among female worker, and of the person going in for textile, commercial was $0.52/10^6$ (RR=0.05), $3.76/10^6$ (RR=0.36).

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Cumulative Tar Exposure

A New Index for Estimating Lung Cancer Risk Among Cigarette Smokers

Edith A. Zang, Ph.D., and Ernst L. Wynder, M.D.

A new index for estimating lifetime exposure to tar from cigarette smoking was found to be the best measure of the relative risk for Kreyberg type I (KI) and Kreyberg type II (KII) lung cancer in a case–control study of 2296 cases (1274 KI and 1022 KII) and 4667 controls. There is a steep, near-linear dose–response of lung cancer risk of both histologic types to cumulative exposure to tar, although the odds ratios are three to five times higher for KI than for KII. The odds ratios for lung cancer in women are consistently higher than those in men with the same level of exposure to tar, particularly among long-term smokers who smoke heavily. Based on their estimates of odds ratios associated with tar exposure, the authors projected an approximate 15–20% decrease in KI lung cancer risk among long-term smokers who smoked heavily for every 10-mg decrease in tar in the cigarettes they smoked. *Cancer* **1992; 70:69–76.**

Key words: dose–response, Kreyberg I and Kreyberg II lung cancer, odds ratio, tar yield, pack-years.

The risk of cancer is obviously influenced by the dose of a carcinogen. The fact that this applies to tobacco smoke as well was established decades ago.[1,2] We also learned early on that the epidemiology of lung cancer in terms of susceptibility to tobacco smoke and possibly other factors differs according to sex and histologic type.[1–5] In this study, we evaluate the effect of lifelong tar exposure on the risk for lung cancer according to histologic type and sex.

From The American Health Foundation, Division of Epidemiology, New York, New York.

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Through our analyses, we re-examine the relative risk of the histologically characterized Kreyberg type I (KI) (squamous, epidermoid, oat, and small and large cell cancers) and Kreyberg type II (KII) (adenocarcinoma) lung cancers in relation to lifetime exposure to cigarette tar and attempt to quantify the decrease in risk of KI lung cancer that may result from smoking cigarettes with lower tar yields. (We used KI and KII terminology recognizing that there may be some epidemiologic variations for each cell type.) We evaluate selected measures of risk from cigarette smoking that have been used by other investigators and compare them with estimates of exposure on the basis of the cumulative tar yield of all cigarettes smoked.

We believe our index of lifelong tar exposure is a comprehensive estimate of risk related to the major tobacco carcinogen (tar) because, in addition to the number of cigarettes smoked, it takes into account the substantial variation in tar yield among the different brands and the chronologic changes in the smoking habits of each individual.

Methods

The data were derived from a large data base collected for an ongoing hospital-based case–control study of tobacco-related cancers that was conducted in 26 hospitals in 6 cities in the United States.[3]

This study included 1274 patients with KI (813 men and 461 women) and 1022 with KII (567 men and 455 women) lung cancer admitted to the participating hospitals from 1981–1988. The KI cases included squamous cell, large cell, oat, and small cell carcinoma, whereas the KII cases included adenocarcinoma and alveolar cell carcinoma. The 4667 controls (2828 men and 1839 women) were selected from among patients with non-tobacco–related diseases and were matched to the cases according to age, sex, race, and time of admission. All data were collected using a detailed, standardized questionnaire that was completed by trained interviewers

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and included information on demographic factors, smoking history, medical history, and diet.[3] Smoking history included information on the brand of cigarette smoked, number of cigarettes smoked per day, and number of years each brand was smoked. The questionnaire had space for patients admitted from 1981–1984 to list up to four different brands of cigarettes, and for those admitted later to list up to seven. If the number of different types of cigarettes smoked exceeded these numbers, the tar yield and cigarettes smoked per day (CPD) were averaged over the brands that were not listed individually, and the duration of smoking was summed over them.

Ever smokers were defined as those who had ever smoked cigarettes at least once a day for 1 year. Current smokers were those who had smoked within the past year. Nonsmokers were those who had never smoked cigarettes regularly. Those who smoked pipes or cigars, either alone or in addition to cigarettes, were excluded from the data.

Lifetime exposure to cigarette smoking is estimated using pack-years, nonfilter and filter years, current number of CPD, and tar years.

Pack-years (P) is calculated as the number of cigarettes of each brand smoked per day (C), multiplied by the number of years that brand was smoked (Y). These products are summed over the different brands smoked throughout each participant's lifetime (B), and divided by 20 to convert the total into packs:

$$P = \sum_{i=1}^{B} (C_i \times Y_i \times 1/20).$$

The cumulative index that measures lifetime exposure to tar through cigarette smoking (T) is computed by summing over the different brands smoked (B) the products of tar content in milligrams (t), the number of days that brand was smoked (D), and the number of cigarettes of each brand consumed per day (C). The result is then converted into kilograms:

$$T = \sum_{i=1}^{B} (t_i \times D_i \times C_i) \times 10^{-6}.$$

Data on tar yield for each brand were obtained from the Federal Trade Register for the year 1977 for patients admitted from 1981–1984, and for the year 1988 for patients admitted thereafter.[6] Tar is defined as that portion of the mainstream smoke of a machine-smoked cigarette that is retained on a glass fiber filter, minus nicotine and water.[7]

Lung cancer risk was estimated using odds ratios and their 95% confidence intervals.[8] Adjusted odds ratios were calculated using the generalized Cochran–Mantel–Haenszel statistic.[9] Chi-square tests for trend[10] were conducted to evaluate the dose–response of risk over exposure level.

The data were maintained and analyzed with a VAX 11/750 minicomputer using a VMS operating system (Digital Equipment Corp., Maynard, MA). Statistical computations were performed using SAS software.[11]

Results

Comparison of Cases and Controls

The relative frequencies of race and age were approximately equal in KI and KII cases and controls and in both sexes (Table 1). However, the frequency of KI lung cancer decreased sharply as the level of education increased, especially among men.

Smokers had more than a 20-fold increase in the

Table 1. Case-Control Status According to Demographic Variables

	Men			Women		
	% Controls (n = 2828)	*% KI (n = 813)*	*% KII (n = 567)*	*% Controls (n = 1839)*	*% KI (n = 461)*	*% KII (n = 455)*
Race						
White	93.9	93.1	92.2	94.8	93.3	94.3
Nonwhite	6.0	6.9	7.8	5.2	6.7	5.7
Education (yr)						
< 12	25.2	50.5	29.2	22.2	26.3	20.7
12	27.6	30.9	27.8	39.2	42.0	43.3
13+	47.2	30.6	43.0	38.6	31.8	36.0
Age (yr)						
< 55	28.8	27.0	33.0	35.5	28.2	31.6
55–64	40.6	39.5	38.8	39.8	39.2	35.4
65+	30.6	33.6	28.2	31.8	31.9	33.0
Never smoked	29.0	1.7	6.5	51.1	4.8	13.4
Smoker	71.0	98.3	93.5	48.9	95.2	86.6

KI: Kreyberg type I; KII: Kreyberg type II.

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Table 2. Age-Adjusted Odds Ratios for Kreyberg Type I Lung Cancer

Measure of exposure to cigarette smoking	Men				Women			
	Quitters		*Current smokers*		*Quitters*		*Current smokers*	
	No.	*OR*	*No.*	*OR*	*No.*	*OR*	*No.*	*OR*
Cumulative tar exposure (kg)								
1–2	376	7.3	243	17.3	219	7.9	325	23.1
3–5	276	19.9	348	29.7	76	15.3	225	47.6
6–8	173	20.0	306	38.7	31	33.2	115	58.9
9+	169	38.3	374	60.2	33	22.9	69	102.9
Pack-years								
1–19	482	3.3	122	4.9	288	2.4	152	11.3
20–39	410	10.6	358	22.8	134	14.2	275	28.6
40–49	258	30.1	421	33.7	86	21.8	232	64.8
50+	259	37.7	485	60.9	49	32.3	120	92.2
Most recent CPD								
1–10	120	4.1	172	14.4	103	1.2	138	7.5
11–20	261	9.0	461	22.3	95	13.8	315	33.6
21–40	254	16.6	537	41.4	64	14.2	271	76.0
41+	172	23.5	218	74.0	22	12.4	57	153.9

OR: odds ratio; CPD: cigarettes smoked per day.

frequency of KI cancer, but only a 6-fold to 7-fold increase in the frequency of KII lung cancer when compared with those who had never smoked. When smokers at the lowest exposure levels are used as the reference group instead of those who had never smoked, the age-adjusted odds ratios for KI over increasing levels of tar exposure range from 2.3–4.5 for men and from 2.7–5.2 for women. For KII lung cancer the dose–response is substantially weaker, with odds ratios of 1.5–2.2 for men and 2.0–2.2 for women.

Association Between Lung Cancer and Exposure to Cigarette Smoking

Tables 2 and 3 summarize the risk of lung cancer associated with various measures of exposure to cigarette smoking. The odds ratios are adjusted to factor out the potential confounding effect of age with extent of exposure.

Tar exposure, pack-years, and current CPD all exhibit dose–responses, suggesting the presence of a

Table 3. Age-Adjusted Odds Ratios for Kreyberg Type II Lung Cancer

Measure of exposure to cigarette smoking	Men				Women			
	Quitters		*Current smokers*		*Quitters*		*Current smokers*	
	No.	*OR*	*No.*	*OR*	*No.*	*OR*	*No.*	*OR*
Cumulative tar exposure (kg)								
1–2	373	2.6	305	6.5	223	3.2	333	8.3
3–5	239	4.4	300	6.5	74	4.8	218	15.1
6–8	165	6.2	259	10.1	27	8.5	86	11.6
9+	105	7.3	278	12.8	21	6.8	42	16.3
Pack-years								
1–19	460	1.3	140	4.6	309	2.1	160	4.9
20–39	428	4.0	335	6.1	141	6.1	265	8.8
40–49	149	6.2	368	9.1	81	12.5	198	16.9
50+	219	8.8	358	13.0	42	7.8	94	22.6
Most recent CPD								
1–10	117	1.0	160	3.9	113	2.2	145	3.6
11–20	261	3.5	421	6.0	95	5.0	292	9.3
21–40	246	5.6	466	10.3	65	5.4	241	20.5
41+	213	4.6	155	15.8	19	1.8	42	30.5

OR: odds ratio; CPD: cigarettes smoked per day.

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cause-and-effect relationship with risk for both histologic types of lung cancer.

The relationship between cigarette smoking and lung cancer is considerably less pronounced for KII than for KI. The odds ratios for quitters are substantially lower than those for current smokers, particularly at the highest levels of most recent CPD. Generally, women exhibit a higher risk for lung cancer of both histologic types at every level of exposure.

The age-adjusted odds ratios for tar exposure in current smokers are presented in Figure 1 according to sex and histologic type. The dose–response curves demonstrate that not only are the odds ratios for KI higher in women, but the difference between the sexes is greatest at the higher exposure levels (23–103 in women, compared with 17–60 in men). The corresponding difference in odds ratios is small for KII (8–16 in women and 7–13 in men).

Table 4 summarizes the differences in smoking patterns and the trends in cigarette smoking over time according to sex. The lower incidence of lung cancer in women[12] is clearly related to the fact that, on the average, women start smoking at a later age (20 versus 17 years), smoke fewer cigarettes per day (21 versus 27), and chose brands with lower tar yield (15 versus 18 mg per cigarette). Nevertheless, smoking is more common among women than men, and women are less likely to quit.[13] As demonstrated by the age-specific incidences of lung cancer listed in Table 4,[14] the differences in incidence of lung cancer between the sexes are gradually reduced in the younger age groups from a male to female ratio of 3.8 at 70 years of age or older, to 2.0 at 50–59 years of age. This apparent cohort effect on relative risk follows the gradual increase in the number of women who are smoking compared with men that has been observed over the past few decades. However, women continue to smoke fewer cigarettes and their substantially higher rate of lung cancer, as shown for the years 1974–1985,[12] clearly exceeds the rate of change in their smoking behavior observed over time. In particular, the nearly three-fold increase in the relative frequency of the small cell histologic type in women, compared with no change in men,[15] is disproportionate to the earlier change in the male to female ratio for smoking exposure, as reflected by the concurrent estimates.[13]

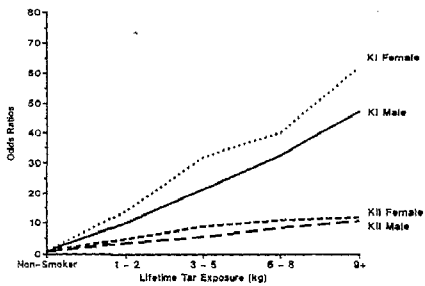

Figure 1. Age-adjusted odds ratios for lifetime tar exposure in current smokers were computed according to sex and histologic type, with a group who never smoked used as the reference group.

In long-term smokers who have smoked for 30 or more pack-years, the projected reduction in risk for both types of lung cancer associated with every 10-mg decrease in tar yield per cigarette ranges between 15–20% (Fig. 2). However, the actual impact on disease prevalence is not as great for KII because the associated risk for this type of lung cancer is less than one-third of that for KI. Similarly, the proportionate decrease in odds ratios is expected to be greater among women than men because the latter appear to be less affected by exposure to tar.

Figure 3 shows the remaining dose–response of KI lung cancer risk over lifetime exposure to tar for current smokers, with four commonly used estimates of smoking exposure held constant at high levels: more than 30 years of smoking filter and nonfilter cigarettes, more than 40 pack-years of smoking, and more than 20 cigarettes currently being smoked per day.

Overall, the odds ratios are higher and the residual dose–response over lifetime exposure to tar is stronger in women than in men. The effect of increasing tar intake among those who smoke heavily is clearest when measured in those who smoke 21 cigarettes per day or more and long-term smokers of filter cigarettes. The dose–response in those who have smoked for 41 or more pack-years and long-term smokers of nonfilter cigarettes is clear only at the highest levels of tar exposure. Figure 3 indicates a twofold to fourfold difference in the odds ratio for KI lung cancer among those who smoke heavily, depending on their cumulative lifetime intake of tar.

Table 5 compares the age-adjusted estimates of dose–response in odds ratios for KI lung cancer among current smokers, with three measures of exposure held constant: lifetime tar, pack-years, and CPD. Both lifetime tar and pack-years exhibit a strong residual dose–response for both sexes; however, the clear trend over CPD shown in Table 3 is now largely cancelled out by the effects of the other two measures of exposure.

Discussion

Effect of Cumulative Tar Exposure

Of the various indices of exposure to cigarette smoking examined, lifelong exposure to tar represents the most

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Table 4. Cigarette Smoking and Lung Cancer Trends by Sex

	Men	Women	Ratio (men to women)
Cigarette smoking			
Age began ($\bar{x} \pm$ SD)	17 ± 5	20 ± 6	0:9
CDP ($\bar{x} \pm$ SD)	27 ± 13	21 ± 13	1:3
Tar in mg/cigarette ($\bar{x} \pm$ SD)	18 ± 6	15 ± 6	1:2
Current smokers (%)*			
1974	42	31	1:4
1985	32	27	1:2
Quitters (%)*			
1974	41	32	1:3
1985	49	43	1:1
Never smoked (%) (55 years of age or older)	21	39	0:5
Lung cancer			
Incidence (per 10^5)†			
1974	74	20	3:7
1985	82	36	2:3
Age-specific incidence‡ (per (10^5) 1981–1985)			
50–59 yr	253	124	2:0
60–69 yr	366	157	2:3
70+ yr	522	138	3:8
Distribution by histologic type§ (%)			
Small cell,			
1974			
1985			
Large cell			
1974	18	8	2:3
1985	17	30	0:6
Squamous	11	26	0:4
1974	19	7	2:7
1985	50	29	1:7
Adenocarcinoma	37	23	1:6
1974	20	37	0:5
1985	27	40	0:7

SD: standard deviation; CPD: cigarettes smoked per day.
* Fiore *et al.*[13].
† SEER data.[12]
‡ SEER data.[14]
§ El-Torky *et al.*[15]

comprehensive estimate of lung cancer risk associated with cigarette smoking.

Pack-years, a commonly used estimate of exposure, fails to account for the large difference in tar content among various brands. The discrepancy in risk estimates between pack-years and tar exposure is expected to broaden with time because an increasing proportion of smokers will have had the opportunity to smoke the low-yield cigarettes for an adequate number of years to have an effect on risk.

Risk estimates based on years of smoking filter versus nonfilter cigarettes, or their ratio,[16,17] also fail to consider the ever increasing variation in tar content within each category. These measures do not account for the individual differences in the number of CPD. In fact, as indicated by the results of several previous investigations,[18–20] a number of those who switch from high-yield to low-yield cigarettes are likely to increase their daily cigarette consumption, which tends to inflate risk estimates based only on the duration of smoking low-yield cigarettes.

CPD is inadequate as a measure of lung cancer risk, whether using the most recent level or averaging over a given number of years, because duration of exposure is an essential component of risk that cannot be ignored. This is demonstrated by the finding that ever smokers have lower risks than current smokers. Apparently, because ever smokers include both recent and longtime quitters, their average duration of smoking is expected to be shorter than that of current smokers.

Exposure to tar has been estimated by several previous investigators, notably Hammond et al.,[21] Lubin et al.,[22] Kunze and Vutuc,[23] Kaufman et al.,[24] and Stellman and Garfinkel.[25] Some of these investigators used

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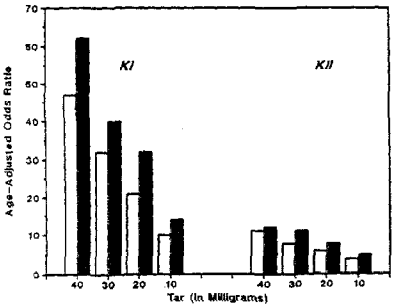

* After 30 pack-years

Figure 2. The age-adjusted odds ratios obtained for lifetime tar exposure were used to compute projected odds ratios for KI and KII lung cancer in men and women. The estimates assume 30 pack-years of cigarette smoking at various levels of tar yield, ranging from 10–40 mg per cigarette. □:Males; ■:females.

grouped levels of tar based on the most common brand smoked by each individual, without including measures of duration or the number of CPD of each brand.[21,22] Others calculated tar exposure by including CPD and duration of smoking, but categorized tar content as low, medium, or high instead of using the actual number of milligrams per cigarette.[21,23] Still others based categories of tar yield on the brand "usually" smoked; they controlled for CPD by categorizing them into grouped intervals, or alternated between the average tar content of every brand smoked by an individual and the tar content of brands smoked for a minimum of 10 years.[24]

The index of lifelong exposure to tar introduced here is unique because it incorporates the duration (in years) and the number of cigarettes smoked of each brand, multiplied by the amount of tar delivered in the smoke of each brand. Thus, the risk estimate reflects the total amount of tar available for inhalation to each individual during his or her lifetime.

Our finding that tar yield retains a strong residue of dose–response in KI lung cancer risk, even when other measures of exposure are held constant (Fig. 3), underscores that the difference in lung cancer incidence among long-term smokers who smoke heavily is, to a great extent, related to the difference in cumulative tar intake. For example, the steep dose–response over tar intake in long-term filter and nonfilter cigarette smokers indicated in Figure 3 reflects the wide individual variation in CPD and tar yield. The equally steep dose–response over tar intake among smokers of at least 21 CPD, however, is largely a reflection of differences in duration and type of cigarettes smoked. A dose–response also is present when pack-years are held constant because, although this measure incorporates both duration and CPD, it fails to allow for variations in tar yield. Furthermore, as mentioned above, because much time has passed since the introduction of low-yield brands, the reliability of pack-years as a measure of lung cancer risk will continue to diminish. The dose–response for KI lung cancer risk to CPD is largely obliterated by the effects of lifetime tar and pack-years (Table 5) because both duration and tar yield are omitted from this measure of exposure. Tar yield and pack-years both retain a clear residue of dose–response: one reflects the effect of cumulative tar intake and the other reflects the effect of duration of exposure.

Male/Female Differences in Risk

A consistent result that emerged from our analyses was that, given the same level of cigarette smoking exposure, the risk of both types of lung cancer, but especially of KI, is consistently higher for women than for men. The age-adjusted odds ratios (Table 3) are approximately one and one-half to two times higher in women than in men at the various levels of pack-years and lifelong exposure to tar and for both histologic types. The dose–response in odds ratios over lifelong exposure to tar, *at constant levels of duration of smoking* nonfilter and filter cigarettes, pack-years, and CPD, is far stronger in women than in men (Fig. 3); this suggests a greater susceptibility to the carcinogenic effect of tar itself.

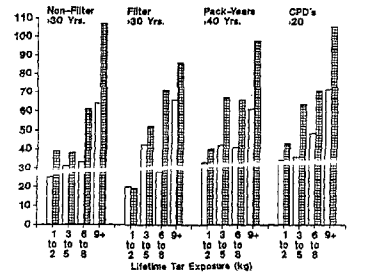

Figure 3. The residual dose–response in odds ratios for KI lung cancer over lifetime exposure to tar from cigarette smoking is estimated in current smokers, with four commonly used estimates of smoking exposure held constant: 30 or more years of smoking nonfilter or filter cigarettes, more than 40 pack-years of smoking, and 21 or more cigarettes currently being smoked per day. Separate estimates are computed for men and women. □:Males; ■:females.

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Table 5. Age-Adjusted Dose–Response Effect on Kreyberg Type I Lung Cancer With Other Exposures Held Constant

Lifetime tar (kg)	At ≥ 20 pack-yr		At ≥ 10 CPD		Pack-years	Lifetime tar ≥ 3 kg		At ≥ 10 CPD		CPD	Lifetime tar ≥ 3 kg		At ≥ 20 pack-yr	
	No.	*OR*	*No.*	*OR*		*No.*	*OR*	*No.*	*OR*		*No.*	*OR*	*No.*	*OR*
Men														
1–2	359	26.9	289	8.4	1–19	31	6.3	187	3.3	1–10	245	39.8	341	35.7
3–5	549	26.3	327	25.1	20–39	399	18.1	461	15.4	11–20	296	29.0	516	24.0
6–8	380	30.1	223	32.2	40–59	437	31.6	458	32.4	21–40	336	35.2	637	33.6
9+	420	48.4	255	48.9	60+	513	52.4	550	50.7	41+	173	38.9	316	42.1
Women														
1–2	240	29.5	197	27.4	1–19	15	6.6	100	10.7	1–10	134	34.1	198	36.3
3–5	208	33.9	92	35.9	20–39	128	22.4	249	8.2	11–20	88	42.7	272	28.6
6–8	118	42.7	64	45.5	40–59	174	18.2	198	51.3	21–40	85	45.9	233	45.4
9+	81	48.3	36	67.1	60+	105	64.1	115	71.5	41+	19	38.5	57	58.8

OR: odds ratio; CPD: cigarettes smoked per day.

The data in Table 4 suggest that the steady increase in lung cancer incidence observed during the past few decades is more pronounced in women than in men. This difference in time trends cannot be adequately explained by the continued, reduced exposure to cigarette smoking among women relative to men. Whereas the male to female ratio for smoking prevalence, as reflected in the data for 1974–1985, has declined from 1.4 to 1.2, the ratio for lung cancer incidence has declined even more (from 3.7 to 2.3). The relative frequency of small cell carcinoma, the histologic type that is most directly related to smoking, has shown a nearly fourfold increase in women but has remained stable in men during the same time period. Although it is true that the difference in smoking exposure between the sexes has been steadily diminishing, the corresponding difference in lung cancer risk has been decreasing even faster. All of this suggests that women may have a lower threshold for the carcinogenic effect of tobacco smoke.

Potential explanations for this gender-related difference in lung cancer risk may include hormonal, reproductive, and dietary differences, or the observed lower reliability in the responses of women to various items in the questionnaire.[26] Early exposure cannot be a factor because men, on the average, start smoking at a younger age (17 versus 20 years). Difference in body size appears to be unrelated to lung cancer in men[27] and, therefore, could not account for the gender-specific differences in risk.

Differences in Histologic Type

Our data confirm the well-known difference in the attributable risk of cigarette smoking for KI versus KII lung cancer. The associated odds ratios are three to five times lower for KII than for KI. The observed dose–response for KII still implies a cause-and-effect relationship to tar exposure. Thus, lowering tar yield should also reduce the risk for KII, although to a lesser extent.

Limitations of the Data

The tumorgenic effect of tar is clearly cumulative. The proposed tar yield index appears to provide the best estimate of lung cancer risk among smokers. Nevertheless, our results should be qualified on several accounts.

First, the tar yield estimates mentioned in this report were based on figures reported by the Federal Register in 1977 for the earlier data, and 1988[6] for the most recent data. No allowance was made for changes in tar yield that have occurred in specific cigarette brands during the smoking history of each individual. In fact, the average tar and nicotine yield of cigarettes has decreased by more than 50% during the past three decades, and significant changes even affected the chemistry of the smoke of specific brands.[28–30] Therefore, the risk among long-term smokers who smoke heavily is underestimated by our measure of cumulative tar exposure, particularly if those who smoke heavily tend to smoke cigarettes with higher tar yields. We are currently assembling data on the historical tar and nicotine levels of each brand. In future analyses, we will be able to measure lifelong exposure to tar more accurately by linking each brand smoked with its chronologically appropriate tar yield.

Second, exposure is affected by depth and frequency of inhalation, puff volume, and butt length. Accurate, retrospective information on these measures would have improved the validity of our risk estimates, particularly among those who have switched to low-yield cigarettes and who may attempt to compensate for the resultant loss of nicotine.[19–21]

Third, we classify cases of lung cancer as KI or KII because of past limitations of our data regarding the coding of histologic type. Since 1985, we have substi-

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tuted the International Classification of Disease (ICD) coding system, which allows us to classify our cases more precisely.

Finally, despite the efforts of skilled interviewers, our data on smoking history are expected to be subject to the usual biases related to differential recall among cases versus controls, lack of knowledge, and wishful thinking on the part of the participants. However, recent testing, through repeat interviews, of the responses recorded in our data shows a high level of internal consistency.[26]

Additional studies are needed to estimate the risk of cancer of the oral cavity, larynx, pancreas, bladder, and esophagus, as well as the risk of other smoking-related conditions such as cardiovascular disease and emphysema. Previous studies have shown no enhanced risk for the development of cardiovascular disease related to low tar/nicotine cigarettes, despite a tendency to compensate for nicotine. Regarding the risk of neoplastic disease, the tar to nicotine ratio requires particular attention. The cumulative, lifelong tar exposure index introduced here can also be effectively applied to relative risk and dose–response estimations related to other cancer sites.

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Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality

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Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. P. Lange, J. Nyboe, M. Appleyard, G. Jensen, P. Schnohr.
ABSTRACT: Data from The Copenhagen City Heart Study, a prospective population study, were analysed to investigate the influence of the type of tobacco and inhalation on pulmonary and total mortality.

The study sample comprised 6,511 men and 7,703 women, selected randomly after age-stratification from the general population. There were 2,986 plain cigarette smokers, 3,222 filter cigarette smokers, 1,578 smokers of cheroots/cigars, 433 male pipe smokers and 773 subjects smoking more than one type of tobacco.

From 1976 until the end of 1989, 2,765 subjects died. Lung cancer was considered as main death cause in 268. Chronic obstructive pulmonary disease (COPD) was considered as the main cause in 94 cases and main or contributory cause of death in 195 cases (COPD related mortality). Current smokers had a higher risk of total mortality compared to lifetime nonsmokers: the relative risks (RR) ranged between 1.2 for male pipe smokers and 2.4 for female plain cigarette smokers. With regard to lung cancer mortality, the RR ranged between 4.1 for male pipe smokers and 7.9 for female plain cigarette smokers. Even higher RR values were estimated for COPD related mortality.

In both sexes, the RR for the investigated end-points were lower in cheroot/cigar smokers and in pipe smokers than in cigarette smokers, but these differences were markedly diminished after an adjustment for the inhalation habit.

The present study substantiates the view that tobacco smoking increases pulmonary and total mortality. The small differences between the various types of tobacco are probably caused by different inhalation patterns.
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In western countries, tobacco smoking is the principal cause of death from lung cancer and from chronic obstructive pulmonary disease (COPD) [1, 2]. In many large surveys, the relative risks of mortality from lung cancer and COPD in cigarette smokers compared to lifetime nonsmokers have been estimated [3]. However, relatively few studies have analysed possible differences between the effects of different kinds of smoking tobacco [4, 5], the main reason being that even large epidemiological studies often comprise relatively few persons smoking other kinds of tobacco than cigarettes.

Recently, a Swedish study of more than 25,000 male smokers estimated that mortality in pipe and cigar smokers may be as high as in cigarette smokers [6]. This observation is in contrast with earlier US and UK studies. The Swedish investigators suggested that the very high mortality risk in Swedish pipe smokers may be caused by the high prevalence of inhalation [6]. The purpose of the present investigation was to analyse mortality from primarily lung cancer and COPD. As the inhalation pattern may be of importance to the effect of smoking on mortality, this was also included in the analyses. Because there are several problems with the determination of the exact cause of death, especially in the case of deaths from non-neoplastic lung diseases [7], we included analyses of total mortality and the so called "COPD-related mortality", *i.e.* all deaths where COPD was listed on the death certificate as either the main or contributory cause of death.

Methods

Population and registration of causes of death

In 1976, a prospective epidemiological study, The Copenhagen City Heart Study, was initiated. The participants were selected among 90,000 persons living in

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19,698 subjects, aged 20 yrs or more, was selected at random. The sample fraction was highest (50%) for persons aged 40–69 yrs. A total of 14,223 subjects (74% of those invited) attended. Details on the selection procedure and a description of the nonresponders have been given previously, together with the questionnaire and the complete examination programme [8, 9].

The population sample described in the present paper comprised 6,511 men and 7,703 women. The nine female pipe smokers were excluded as the number of end-points in this group was too small for separate analysis. The subjects were followed until the end of 1989. Notification of deaths and causes of death was obtained from the Central Death Register from the National Board of Health. In Denmark, a physician, preferably the one who knew the patient's course best, must complete a death certificate at every death. The death certificate contains the assumed causes of death: always the underlying cause and in many cases also a secondary and a tertiary cause. The underlying cause is defined as a disease or injury which initiated the train of events leading directly to death, whereas the secondary or tertiary causes describe a disease (often a disease which may follow the underlying cause) which in some way could have contributed to death. The coding of deaths is performed centrally in the Death Register, based on the information stated on the death certificates. Death from lung cancer (code no. 162) was registered according to the 8th revision of the International Classification of Diseases (ICD) classification, which is still used in Denmark [10]. As the number of deaths from COPD was small in different smoking groups after stratification for sex, we mainly analysed the COPD-related mortality, which comprised the cases where chronic bronchitis or emphysema (codes no. 490–492) were considered as the underlying or as a contributing cause of death.

Smoking habits

The participants reported whether they were current smokers, ex-smokers or lifetime nonsmokers. Both current and ex-smokers reported the duration of smoking, whereas only current smokers reported their daily tobacco consumption, the type of tobacco smoked, and whether they inhaled or not. The subjects were not asked if they had smoked different types of tobacco in the past. No information on the depth of inhalation was obtained. The following groups of smokers were generated for the analyses:

NS: lifetime nonsmokers - subjects who at the enrolment reported that they had never smoked tobacco;
EX: ex-smokers - former smokers who ceased smoking more than one year prior to the examination;
CIGP: subjects smoking only plain (non-filter) cigarettes at enrolment;
CIGF: subjects smoking only filter cigarettes at enrolment;
CER: subjects smoking only cheroots, cigars or cigarillos at enrolment;
PIPE: men smoking only a pipe at enrolment;
MX: subjects who smoked more than one type of tobacco at enrolment.

To estimate the magnitude of current tobacco consumption, the following equivalents for the tobacco content were used: one plain or filter cigarette = 1 g; one cigar = 5 g; one cheroot or cigarillo = 3 g; one g of pipe tobacco = 1 g. For subjects who smoked more than one type of tobacco, the total amount of tobacco smoked per day was chosen as a measure of current tobacco consumption. For current smokers, an estimate of lifetime tobacco consumption was calculated as pack-years (current tobacco consumption ($g \cdot day^{-1}$) multiplied by the duration of smoking (yrs) and divided by 20).

Statistical analysis

The subject of the analysis was the intensity or instantaneous risk of death. We used the regression model of Cox [11]. Time was reckoned from the initial examination until the investigated endpoint (event), death from other causes (censoring) or until the end of the observation period. The regression coefficients were estimated using the maximum likelihood method as suggested by Cox. Smoking groups and inhalation were included as binary variables, as they only had two outcomes, whereas age was included directly as a quantitative variable.

The question of first order interactions between the covariates was investigated by comparison of regression models with and without interaction terms using the maximum likelihood ratio test. No significant interactions were found.

Control of the assumption of proportional hazards through-out the follow-up period was performed by plotting the logarithm to the cumulated hazard in different subgroups (strata) against time of observation. The distance between the curves in different smoking groups appeared to be the same throughout the period for all causes of mortality. For COPD-related mortality and lung cancer the curves for current smokers were parallel. However, the mortality in ex-smokers seemed relatively lower towards the end of the observation period, but because of the small number of deaths in this group a detailed analysis was not possible.

Separate regression models were employed for the three investigated end-points: death from all causes, death from lung cancer and COPD-related death. In all analyses, age was included as covariate and in the analyses comprising current smokers only, pack-years were also included in the model. Separate regressions were performed for men and women. In men, all the previously defined smoking groups could be analysed, whereas, in women, a sufficient number of end-points was only observed in the following groups: NS, EX, CIGP, CIGF and CER.

In the tables, the estimated relative risks (RR) and the 95% confidence intervals (95% CI) are given. If the 95% CI includes 1.0, the RR in this smoking group is not significantly different from the baseline group at the 5% level.

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On the basis of the RR in various groups of smokers relative to lifetime nonsmokers, we have calculated the population attributable risk of smoking, that is the proportion of the risk that may be attributed to smoking in subgroups of the population [12].

age. The relative risks (RR) of total and pulmonary mortality in all smoking groups were >1. Generally, the RR were higher in women than in men, especially with regard to COPD related mortality.

Table 1. – General characteristics of the subjects according to smoking group

	Women						Men						
Smoking gp	NS	EX	CIGP	CIGF	CER	MX	NS	EX	CIGP	CIG	CER	PIPE	MX
n	2159	1089	1344	2269	770	72	721	1253	1642	953	808	433	701
Age yrs	54	54	51	49	60	50	49	56	52	48	59	54	53
	(13)	(12)	(10)	(11)	(10)	(13)	(15)	(12)	(11)	(12)	(11)	(12)	(12)
Pack yrs	0	0*	19	15	25	23	0	0*	29	24	40	28	39
	(0)	(0*)	(11)	(11)	(16)	(17)	(0)	(0*)	(18)	(16)	(26)	(20)	(22)
Smoking duration yrs	0	16	28	24	29	26	0	25	34	29	39	35	35
	(0)	(12)	(10)	(12)	(13)	(12)	(0)	(14)	(12)	(12)	(14)	(14)	(13)
Inhalation %	0	0*	85	77	25	56	0	0*	93	91	42	56	75

Inhalation is given as a frequency whereas the other variables are given as arithmetical means. For definition of smoking groups see text. Data for age, pack-years and smoking duration are given as mean with SD in parenthesis. *: no information available regarding earlier inhalation pattern.

Table 2. – Mortality according to the smoking habit and sex

	Women						Men						
Smoking gp	NS	EX	CIGP	CIGF	CER	MX	NS	EX	CIGP	CIGF	CER	PIPE	MX
n	2159	1089	1344	2269	770	72	721	1253	1642	953	808	433	701
Mortality													
Total	262	133	224	241	185	10	115	318	476	206	326	115	154
(%)	(12)	(12)	(17)	(11)	(24)	(14)	(16)	(25)	(29)	(22)	(40)	(27)	(22)
Lung cancer	7	8	20	19	14	0	5	21	65	25	47	16	21
(%)	(0.3)	(0.7)	(1.5)	(0.8)	(1.8)	(0)	(0.7)	(1.7)	(4.0)	(2.6)	(5.8)	(3.7)	(3.0)
COPD	2	6	6	13	4	0	2	14	24	12	4	2	5
%	(0.1)	(0.6)	(0.4)	(0.6)	(0.5)	(0)	(0.3)	(1.1)	(1.5)	(1.3)	(0.5)	(0.5)	(0.7)
COPD-related	3	11	12	22	10	1	3	25	43	23	22	7	13
%	(0.1)	(1.0)	(0.9)	(1.0)	(1.3)	(1.4)	(0.4)	(2.0)	(2.6)	(2.4)	(2.7)	(1.6)	(1.9)

For definition of smoking groups see text. %: percentage of all subjects in the smoking group. COPD: chronic obstructive pulmonary disease.

Results

The distribution of the subjects according to sex and smoking group at the time of enrolment in the study is given in table 1. On average, men and women smoking cheroots/cigars were older and had a higher cumulative tobacco consumption than other smokers. Plain cigarette smokers reported inhalation more frequently than did smokers in the other groups.

The distribution of deaths by sex and smoking group is given in table 2. Generally, the frequency of all investigated end-points was higher in smokers than in lifetime nonsmokers, regardless of the type of tobacco smoked. Similar trends were observed in both sexes.

The results of the Cox regression analysis focusing the risk of total and pulmonary mortality in smokers smoking different types of tobacco, compared to the risk in lifetime nonsmokers, are given in table 3. The risk of death increased significantly with

Table 3. – Relative risks (RR) of mortality by smoking status with NS as the baseline group

Smoking group	Total mortality RR (95% CI)	Lung cancer mortality RR (95% CI)	COPD-related mortality RR (95% CI)
Women			
NS	1.0	1.0	1.0
EX	1.2 (1.0–1.4)	3.4 (1.1–11)	11 (2.5–53)
CIGP	2.4 (2.0–2.9)	7.9 (2.9–21)	15 (3.1–65)
CIGF	1.7 (1.4–2.1)	4.8 (1.7–13)	16 (3.6–70)
CER	1.8 (1.4–2.2)	4.9 (3.0–12)	10 (2.3–48)
Men			
NS	1.0	1.0	1.0
EX	1.1 (0.9–1.4)	2.1 (0.7–6.0)	3.0 (0.9–10)
CIGP	1.9 (1.6–2.4)	7.3 (2.6–20)	6.4 (2.0–20)
CIGF	1.8 (1.4–2.3)	6.0 (2.2–19)	7.9 (2.3–27)
CER	1.6 (1.3–2.0)	6.0 (2.2–17)	3.7 (1.1–12)
PIPE	1.2 (0.9–1.6)	4.1 (1.4–13)	2.4 (0.6–9.6)
MX	1.2 (0.9–1.6)	4.5 (1.6–13)	4.3 (1.2–15)

Derived from regression models of Cox including age as covariate. NS: lifetime nonsmokers; For definition of smoking groups see text. 95% CI: 95% confidence interval; COPD: chronic obstructive pulmonary disease.

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The differences in mortality between smokers of plain cigarettes and those smoking other types of tobacco, after adjustment for age and pack-years, are shown in table 4. With regard to total mortality the RR in plain cigarette smokers was higher than in the other groups, especially in women. With regard to pulmonary mortality, none of the differences between plain and filter cigarette smokers were statistically significant.

In women the RR in cheroot smokers were 30–40% reduced compared to smokers of plain cigarettes (table 4).

Table 4. – Relative risks (RR) of mortality in current smokers by the type of tobacco smoked

Smoking group	*Total mortality* RR (95% CI)	*Lung cancer mortality* RR (95% CI)	*COPD-related mortality* RR (95% CI)
Women			
CIGP	1.0	1.0	1.0
CIGF	0.7 (0.6–0.9)	0.7 (0.4–1.4)	1.3 (0.6–1.6)
CER	0.7 (0.6–0.9)	0.6 (0.4–1.3)	0.7 (0.3–0.7)
Men			
CIGP	1.0	1.0	1.0
CIGF	0.9 (0.8–1.1)	0.9 (0.6–1.4)	1.2 (0.7–2.0)
CER	0.8 (0.7–0.9)	0.7 (0.5–1.1)	0.5 (0.3–0.8)
PIPE	0.6 (0.5–0.8)	0.6 (0.3–1.0)	0.4 (0.2–0.8)
MX	0.6 (0.5–0.7)	0.3 (0.1–1.4)	0.2 (0.1–0.6)

Derived from regression models of Cox including age and pack-years as covariates. For definition of smoking group see text. For abbreviations see legend to table 3.

In men, the RR values in pipe and in mixed smokers (MX) were 40–80% reduced compared with cigarette smokers, whereas the RR in cheroot/cigar smokers was inbetween the risk of cigarette smokers and the risk of pipe smokers.

To investigate the importance of reported inhalation pattern on mortality, the following grouping of smokers was employed: cigarette smokers (both plain and filter) who reported inhalation, cigarette smokers who reported no inhalation, smokers of other types of tobacco than cigarettes (cheroot/cigar and pipe) who reported inhalation, and finally smokers of other types of tobacco than cigarettes who reported no inhalation. The RR values of total and pulmonary mortality for these four groups are shown in table 5. Both cigarette and non-cigarette smokers who reported inhalation had a higher risk of death from the investigated end-points than smokers who said they did not inhale. The RR for the investigated end-points for women smoking cheroots and inhaling was significantly higher than for female cigarette smokers who inhaled.

Based on the RR given in table 3 and on the distribution of the different smoking groups we have calculated the attributable risks shown in table 6. The proportion of death that could be attributed to smoking was 0.36 in both sexes. With regard to lung cancer and COPD-related deaths the proportion was more than twice as high. Generally plain cigarette smoking was the highest contributing smoking modality to the deaths from the investigated diseases. However, in women the contribution of filter cigarette smoking to COPD-related mortality was the highest.

Table 5. – Relative risks (RR) of mortality in current smokers by the type of tobacco smoked and inhalation

Smoking group	Total mortality RR (95% CI)	Lung cancer mortality RR (95% CI)	COPD-related mortality RR (95% CI)
Women			
CIGP+CIGF + inhalation	1.0	1.0	1.0
CIGP+CIGF - inhalation	0.7 (0.6–0.9)	0.3 (0.1–0.8)	0.4 (0.2–1.1)
CER + inhalation	1.6 (1.2–2.2)	1.5 (0.5–3.7)	2.1 (0.8–5.3)
CER - inhalation	0.6 (0.5–0.8)	0.4 (0.2–0.9)	0.2 (0.1–0.6)
Men			
CIGP+CIGF + inhalation	1.0	1.0	1.0
CIGP+CIGF - inhalation	0.9 (0.7–1.2)	0.2 (0.1–0.8)	0.5 (0.2–1.4)
CER+PIPE + inhalation	1.0 (0.8–1.2)	1.1 (0.7–1.6)	0.9 (0.5–1.6)
CER+PIPE - inhalation	0.7 (0.6–0.8)	0.4 (0.3–0.6)	0.2 (0.1–0.3)

Derived from regression models of Cox including age and pack-years as covariates. For definition of smoking groups see text. For abbreviations see legend to table 3.

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Table 6. – Estimated proportion of the investigated end-points attributable to smoking and contribution from individual smoking groups

Smoking group	Total mortality		Lung Cancer mortality		COPD-related mortality	
	Women	Men	Women	Men	Women	Men
Attributable proportion to smoking*	0.36	0.36	0.75	0.79	0.90	0.78
Contribution from Subgroups						
EX	0.02	0.02	0.08	0.04	0.15	0.09
CIGP	0.15	0.15	0.29	0.33	0.23	0.30
CIGF	0.14	0.08	0.28	0.17	0.43	0.22
CER	0.05	0.09	0.10	0.13	0.09	0.07
PIPE		0.01		0.04		0.02
MX		0.01		0.08		0.08

For definitions of smoking groups see text.*: including ex-smokers. COPD: chronic obstructive pulmonary disease.

Discussion

We found that smokers, regardless of the type of tobacco smoked, had a higher risk of total and pulmonary mortality than lifetime nonsmokers. This pertained to both men and women. After adjustment for cumulated tobacco consumption, the differences in the mortality risk between plain and filter cigarette smokers were small and statistically significant only in the case of total mortality in women. Compared with cigarette smokers, smokers of cheroots/ cigars and especially pipe smokers had a lower risk of mortality, although the risk was still markedly higher than in lifetime nonsmokers. Both cigarette and non-cigarette smokers who said they inhaled had a higher risk of mortality than smokers who did not inhale.

As for many previous studies, our study suffers from several limitations. The information on lifetime tobacco consumption is incomplete, as we did not ask the participants what kind of tobacco they smoked before enrolment into the study. This information may be especially important in pipe and cheroot/cigar smokers who have previously been smoking cigarettes [5]. We were also unable to include changes in smoking habits during the follow-up in the analyses. Another drawback of the present study is the small number of deaths from COPD in many of the smoking groups. To enlarge the number of end-points, we also analysed the COPD-related deaths. An earlier study has indicated that this approach may be correct [13].

In spite of these apparent limitations, the present study also has advantages: an acceptable attendance of 73.6% of the invited subjects; the very high follow-up rate as only 63 subjects left Denmark and only one was lost during the observation period; the relatively high frequency of smoking other types of tobacco than cigarettes; and, finally, in contrast to the study of CARSTENSEN *et al.* [6], information on the inhalation habits of pipe and cheroot/cigar smokers.

Plain and filter cigarettes compared

Compared with lifetime nonsmokers, cigarette smokers had the highest RR of all the investigated end-points. The RR of total mortality, lung cancer and COPD mortality are similar to earlier results [1–3]. After statistical adjustment for the cumulative tobacco consumption, the RR of pulmonary and total mortality in plain cigarette smokers and filter cigarette smokers were very similar in men. Female filter cigarette smokers had a 30% lower risk of all-causes of mortality and lung cancer mortality, whereas they had a 30% higher risk of COPD-related mortality than smokers of plain cigarettes. Previous studies, have shown that subjects smoking cigarettes with lower tar yields may have a risk of lung cancer which is 5–50% lower than subjects smoking cigarettes with higher tar yields, depending on the study [3, 14, 15]. It is possible that the relatively small difference in lung cancer mortality observed in the present study might be due to the relatively small difference in the tar yields of the cigarettes compared: at the time of our study, the average tar content in Danish cigarettes was 35 mg per cigarette in plain cigarettes and 23 mg per cigarette in filter cigarettes.

The risk of death from COPD is closely related to the level of lung function [13, 16]. As most previous studies have been unable to show a significant benefit from smoking lower-tar cigarettes, compared to high- and medium-tar cigarettes, on lung function and lung function decline [17–19], our results on COPD-related mortality support the theory that tar content of the cigarettes may be relatively unimportant for COPD [17]. In contrast to the observations of The American Cancer Society study [4], the trend observed in the present study suggests that smokers of filter cigarettes may even have a slightly higher risk of COPD than smokers of plain cigarettes.

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Cigar/cheroot and pipe smoking

Compared with lifetime nonsmokers, the estimated RR for mortality was 1.6–1.7 for cheroot/cigar smokers and 1.2 for pipe and mixed smokers. These risks are higher than the values reported by HAMMOND [4] in 1966 in a US population. This may be partly explained by the fact that the US analysis was performed on smokers who had previously only been smoking cigars or pipes. As in earlier European studies, the mortality from lung cancer in cheroot/cigar and pipe smokers in the present study was much higher than in lifetime nonsmokers and only slightly lower than in cigarette smokers [5, 6, 15, 20]. This is in accordance with the experimental results, which show that condensates from pipes and cigars are at least as carcinogenic as condensates from cigarettes [3].

With regard to COPD, the differences between cigarette and non-cigarette smokers were more pronounced than in the case of the lung cancer. The risk of COPD-related mortality in cheroot/cigar and pipe smokers was reduced by approximately 30–50% as compared with cigarette smokers, but it was still much higher than in lifetime nonsmokers. In the study of British doctors, the risk of COPD mortality in pipe and cigar smokers was approximately 10 times higher than in lifetime nonsmokers, although it was only one third of the risk of cigarette smokers [5].

Inhalation

Subjects who reported inhalation had a higher mortality from all of the investigated end-points than those who said they did not inhale. This was especially the case for pulmonary mortality. After adjustment for the inhalation pattern, the differences in mortality between smokers of different types of tobacco were markedly diminished. Thus, not surprisingly, our results indicate that the inhalation of tobacco smoke should be avoided.

With regard to the importance of inhalation to total mortality, the large American Cancer Society Study agrees with our findings [4]. With regard to pulmonary mortality, the importance of inhalation has in the past been subject to some controversy. DOLL and PETO [5] reported a positive association between mortality from COPD and inhalation of tobacco smoke, but a surprising negative correlation between inhalation and lung cancer mortality. The latter finding has been reproduced in another UK survey [21]; however, GARFINKEL and STELLMAN [22] using data from the American Cancer Society Study II reported a higher risk of lung cancer with an increasing degree of inhalation. The discrepancies between various studies suggest that the value of reported inhalation as an index of actual inhalation may be low, especially in cigarette smokers who comprised the vast majority of subjects in the UK surveys. This has also been shown experimentally with measurements of biological inhalation markers [23]. On the other hand, previous studies have shown that the value of self-reported inhalation in pipe and cigar smokers may in fact be quite high and that this information may be even more useful than the knowledge of whether the current non-cigarette smokers had been smoking cigarettes in the past [24, 25]. Our results show that information on inhalation is valuable even if it is not validated by biological markers.

Male-female differences

An analysis focusing on the differences in RR values between sexes (not shown), revealed that the differences were not statistically significant. In Denmark, as in some other European countries, smoking is steadily declining in men, but much less so in women. The latest Danish data show that in young subjects aged 15–20 yrs, smoking is even more prevalent in women than in men [26]. If this trend continues in the future, it is likely that diseases such as lung cancer and COPD will become equally common in both sexes.

Attributable risks

The proportion of the investigated deaths attributable to smoking in the present study is very close to the results of the American Cancer Society 50 State Study [3]. The slightly higher proportion of lung cancer cases in men than in women that could be attributed to smoking is in line with observations that lung cancers in lifetime nonsmokers are more often seen in women than in men [27]. On the other hand, we observed a higher proportion of COPD-related deaths in women than in men that could be attributed to smoking. This could reflect the possible role of occupational exposures to dusts and fumes in men, although differences in the diagnostic criteria of COPD between the sexes could also be responsible for our results.

A calculation of the attributable risks in the subgroups of smokers showed that most of the smoking-related deaths in men could be attributed to plain cigarette smoking. In women, however, filter cigarettes "were responsible" for more COPD-related deaths than plain cigarettes. This reflects the fact that women, more often than men, smoked filter cigarettes and that the RR for COPD-related mortality were higher in filter cigarette smokers than in plain cigarette smokers. Although we found a surprisingly high RR for cheroot/cigar and pipe smokers, the contribution of these types of tobacco to mortality was small, as relatively few subjects smoked these tobacco types. It is likely that this proportion will be even smaller in the future, as smoking cessation rates in this subgroup of smokers are higher than in cigarette smokers [26].

In conclusion, this study shows that although cigarette smokers are at highest risk of death from lung

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cancer and COPD, the differences between cigarette smokers and smokers of other types of tobacco are probably due to different inhalation patterns, and are relatively small compared to the differences between the latter group and nonsmokers.

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A prospective study of cigarette tar yield and lung cancer

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We examined the relationship of cigarette tar yield and other cigarette-usage characteristics in current smokers to the incidence of lung cancer in a study population of 79,946 Kaiser Permanente Medical Care Program members, aged 30-89 years, who completed a detailed, self-administered, smoking-habit questionnaire during the years 1979 through 1985. Mean length of follow-up was 5.6 years. There were 302 incident lung cancers, of which 89 percent occurred in current or former smokers. The tar yield of the current cigarette brand was unassociated with lung cancer incidence (relative risk [RR] = 1.02 per 1 mg tar-yield in men, 95 percent confidence interval [CI] = 0.98-1.05; RR = 0.99, CI = 0.96-1.03 in women). However, in long-term (>20 years) smokers, the risk of lung cancer was decreased in women who had smoked filtered cigarettes for 20 or more years relative to lifelong smokers of unfiltered cigarettes (RR = 0.36, CI = 0.18-0.75), but not in men who had smoked filtered cigarettes for 20 or more years (RR = 1.04, CI = 0.58-1.87).

Key words: Cigarettes, lung neoplasms, tars, tobacco smoking, United States.

Introduction

Although many epidemiologic studies have shown that smokers of cigarettes with relatively low yields of tar have a lower risk of lung cancer than smokers of high tar-yield cigarettes, few have examined the relationship of tar yield to lung cancer in a prospective cohort design.[1-4] Two other cohort studies have shown that smoking filtered cigarettes is associated with lower risk of lung cancer than smoking unfiltered cigarettes, presumably because the tar yield of filtered cigarettes is lower.[5,6] Case-control studies also have found a lower risk of lung cancer to be associated with low-tar or filtered cigarette use.[7-11]

In 1979, we began a prospective study of the health effects of smoking low-yield cigarettes in the members of a large, prepaid, health-care program who underwent multiphasic health checkups (MHCs).[12,13] The results of the follow-up through 1987 for lung cancer in this cohort of nearly 80,000 individuals is reported here.

Methods

Study population and follow-up

The study population is composed of 79,946 Kaiser Permanente Medical Care Program members, aged 30-89 (mean age, 48 years), who completed a detailed, self-administered, smoking-habit, research questionnaire in the setting of a multiphasic health checkup (MHC) conducted in the San Francisco (until 1980) and Oakland Kaiser Permanente facilities in California (United States). The study cohort includes those who completed the questionnaire between its inception in mid-1979 through 1985. Follow-up was carried out for lung cancer from the date of the MHC to the date of the

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earliest of the following: diagnosis of lung cancer ($n = 302$); death ($n = 2,275$); membership termination ($n = 15,454$); or 31 December 1987 ($n = 61,915$). The mean length of follow-up was 5.6 years.

Determination of smoking status and of tar content

Persons were classified as current, former, or never-smokers on the basis of their responses to the smoking-habit questionnaire.[17] Current and former smokers also were questioned about: frequency (number of cigarettes per day) and duration (years) of smoking; brand of cigarette usually smoked; characteristics of cigarette brand (length, filtered or unfiltered, menthol-ated or plain); amount of cigarettes smoked; inhalation habits (frequency and depth of inhalation); and duration (years) of smoking filtered and low-tar cigarettes. The brand of cigarette usually smoked was classified as to tar and nicotine yield according to the Federal Trade Commission Reports.[18-20] The reports of May 1978, March 1981, and March 1983, were used for questionnaires completed before July 1981, July 1981 through December 1983, and January 1984 through December 1985, respectively. The tar yield could not be ascertained for 14 percent of current smokers. The mean tar yield for the brand smoked by current smokers was 14.8 mg.

Source of follow-up data

Determination of lung cancer cases. Incident lung cancers were determined from a summary file of first occurrences of cancer in the Kaiser Permanente Medical Care Program. The main source of cases for this file was the Resource for Cancer Epidemiology, a California state-run and federally supported population-based registry of cancer incidence in the five San Francisco Bay Area counties including Oakland and San Francisco. (The administration changed in 1986 to the Northern California Cancer Center, and the registry is now known as the Bay Area Resource for Cancer Control.) The file also includes cancer cases from the computer-stored records of all overnight hospitalizations in the Northern California Kaiser Permanente Medical Care Program. Cases from the registry were confirmed by registry personnel, while cases determined by hospital discharge diagnosis were confirmed by manual medical-record review.

Mortality. Mortality was ascertained through 1987 by computer-matching the members of the study cohort with the Kaiser Permanente Medical Program membership file as of 1989 and extracting a list of subjects who were no longer members. From this list, we accepted as confirmed deaths, those ascertained in previous studies performed at the Kaiser Permanente Division of Research. The mortality status of the remaining study subjects who were no longer members was ascertained by computer-matching names with the California death file using the California Automated Mortality Linkage and Information System (CAMLIS).[21] Questionable matches were confirmed or excluded by manual record review.

Membership termination data. Annual membership status was determined in June of each year by examination of computerized files. The membership termination date was estimated to be 31 December of the year in which the person last appeared in the June membership file, because that date represents the midpoint between successive June membership updates.

Analytic methods

Statistical analyses were performed using SAS programs.[22] Mantel-Haenzel estimates of the age-adjusted relative risks (RR) of lung cancer associated with current and former smoking were obtained.[23] For each individual, person-years of follow-up were assigned to appropriate age categories using attained age for the duration of follow-up. Incidence rates were age-adjusted by the direct method using the age distribution of current smokers as the standard. Cox proportional hazards models were used to examine the joint effect of multiple sociodemographic and smoking characteristics on the risk of lung cancer.[24] RRs associated with tar yield and selected cigarette-usage characteristics in current smokers were obtained by entering each of these characteristics individually in a proportional hazards model which included age, gender, race, and education, as well as the frequency and duration of smoking.

Results

The prevalence of current smoking was related inversely to age, and was higher in men than in women (Table 1). Among the race categories in this study, the prevalence of smoking was highest in Blacks, followed by Whites, and lowest in Asians. Graduation from college was associated with a lower prevalence of smoking than lesser degrees of education.

There were 302 incident lung cancers in this cohort through 1987, of which 89 percent were in current or former smokers. Age-specific RRs for lung cancer ranged from 11.3 to 34.9 for current smokers (*cf* non-smokers) (Table 2); the age-adjusted RR of lung cancer for current smokers was 12.8 (95 percent confidence

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Table 1. Distribution of cigarette smoking status by age, gender, race, and education (No., with % in parentheses)

	Nonsmoker	Former	Current	Total
Age				
30-49	23,080 (49)	9,457 (20)	14,857 (31)	47,394
50-64	11,156 (48)	5,748 (25)	6,152 (27)	23,056
65-74	4,032 (55)	1,902 (26)	1,391 (19)	7,325
75-89	1,551 (71)	434 (20)	186 (9)	2,171
Gender				
Men	14,413 (41)	9,822 (28)	10,740 (31)	34,975
Women	25,406 (57)	7,719 (17)	11,846 (26)	44,971
Race				
White	21,761 (47)	12,247 (27)	12,212 (26)	46,220
Black	8,986 (45)	3,382 (17)	7,461 (38)	19,829
Asian	6,385 (72)	1,052 (12)	1,454 (16)	8,891
Other/unknown	2,687 (54)	860 (17)	1,459 (29)	5,006
Education				
≤ High school	10,327 (48)	4,085 (19)	6,999 (33)	21,411
Technical/business	2,447 (47)	1,193 (23)	1,552 (30)	5,192
Part college	8,477 (44)	4,384 (23)	6,530 (34)	19,391
College graduate/post	15,878 (54)	7,087 (24)	6,495 (22)	29,460
Unknown	2,690 (60)	792 (18)	1,010 (22)	4,492
Total	39,819 (50)	17,541 (22)	22,586 (28)	79,946

interval [CI] = 8.7-18.7). Age-specific RRs for lung cancer ranged from 4.5 to 7.0 for former smokers; the age-adjusted RR of lung cancer for former smokers was 5.5 (CI = 3.7-8.2).

Frequency and duration of cigarette smoking were related strongly to the incidence of lung cancer in smokers. An increase in smoking frequency of 10 cigarettes per day was associated with a 33 percent increase in the risk of lung cancer ($P < 0.0001$), adjusted for age, gender, race, education, and duration of smoking. A 10-year increase in duration of smoking was associated with a 63 percent increase in the risk of lung cancer ($P < 0.0001$), adjusted for frequency of smoking and the sociodemographic variables. The vast majority of lung cancers were associated with a history of at least 20 years of smoking. The risk of lung cancer in former smokers diminished with increasing length of time since quitting, but was still nearly twice that of nonsmokers in those who quit 15 or more years before the MHC (RR = 1.9, CI = 1.1-3.5).

The RR of lung cancer in current smokers associated with selected cigarette-usage characteristics is shown in Table 3, adjusted for age, race, education, frequency of smoking (cigarettes/day), and duration of smoking (years). The cut-points for tar yield were chosen so that approximately 25 percent of smokers would be in the highest and the lowest categories. Tar content was not significantly associated with the risk of lung cancer in either men or women. Frequency of inhalation (all or most times *of* other categories) was associated with increased risk of lung cancer in women only (RR = 2.1, $P = 0.02$). None of the remaining characteristics was associated significantly ($P < 0.05$) with lung cancer in either men or women. These associations did not change substantially in analyses limited to longer-term smokers, *i.e.*, those with a history of at least 20 years of

Table 2. Incidence of lung cancer by age and smoking status, and relative risk (RR) and 95% confidence interval (CI) of lung cancer in current and former smokers compared with nonsmokers

Age group	Current		Former		Never		Current		Former	
	No. of events	Rate/ 100,000	No. of events	Rate 100,000	No. of events	Rate/ 100,000	RR	(CI)	RR	(CI)
30-49	22	32.7	2	4.8	1	0.9	34.9	(4.7-258.9)	5.1	(0.5-56.7)
50-64	89	224.8	37	110.0	13	19.1	11.8	(6.6-21.1)	5.8	(3.1-10.9)
65-74	54	406.5	27	161.8	12	36.0	11.3	(6.0-21.1)	4.5	(2.3-8.9)
75-89	19	671.3	18	341.6	8	48.5	13.8	(6.1-31.6)	7.0	(3.1-16.2)

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Table 3. Incidence and relative risk (RR) and 95% confidence interval (CI) of lung cancer associated with selected cigarette use characteristics in current smokers

Characteristic	Men				Women			
	No. cases	Rate[a] (per 100,000 person-years)	RR[b]	(CI)	No. cases	Rate[a] (per 100,000 person-years)	RR[b]	(CI)
Frequency of inhalation								
All or most of time	76	143.5	1.12	(0.66-1.89)	63	122.1	2.05	(1.12-3.74)
Other (reference)	20	91.4	—		17	60.8	—	
Depth of inhalation								
Deep	25	203.5	1.44	(0.89-2.34)	6	85.3	0.74	(0.32-1.73)
Other (reference)	71	115.5	—		74	100.3	—	
Amount of cigarettes								
> 3/4 pack	37	132.9	0.98	(0.64-1.50)	29	105.7	1.10	(0.68-1.79)
≤ 3/4 pack (reference)	58	127.2	—		50	91.4	—	
Filter								
Yes	81	136.6	1.03	(0.61-1.75)	74	95.2	0.65	(0.32-1.31)
No (reference)	17	118.0	—		9	217.2	—	
Tar								
< 11 (reference)	14	107.0	—		29	128.5	—	
11-18	39	136.5	1.29	(0.69-2.43)	34	102.7	0.93	(0.55-1.59)
> 18	29	116.9	1.27	(0.67-2.43)	13	86.0	0.67	(0.34-1.32)
Tar (continuous)	N/A	N/A	1.02	(0.98-1.05)	N/A	N/A	0.99	(0.96-1.03)

[a] Age-adjusted rate, adjusted by direct method using the age distribution of current smokers as the standard.
[b] Adjusted for age, race, education, cigarettes/day, and number of years of smoking.

smoking. Though age and duration of smoking were highly correlated (correlation coefficients = 0.77 for men and 0.73 for women), each was associated significantly with lung cancer in the multivariate model, and the relationship of other cigarette-usage characteristics to lung cancer risk was not altered appreciably by the removal of either age or duration of use from the model.

We did not collect historical information about all brands smoked, so we could not ascertain a long-term history of tar yields in brands used by smokers. In order to examine indirectly the relationship of low-yield cigarette use to lung cancer, we examined the relationship of self-reported duration of filtered and of low-tar cigarette smoking to lung cancer incidence in current smokers with a history of at least 20 years of smoking. Duration of filtered cigarette use was related inversely to the risk of lung cancer in women only, adjusted for age, race, education, frequency, and duration of smoking (Table 4). These associations did not change significantly when the proportion of smoking-lifetime, represented by duration of filtered cigarette use, was substituted for years of filtered cigarette use, nor were they altered when the cigarette usage characteristics were entered individually as independent variables into the statistical models. There was a 64 percent decrease in the risk of lung cancer in women who smoked filtered cigarettes for 20 years or longer relative to the risk in women who were lifetime smokers of unfiltered cigarettes. Duration of low-tar cigarette use was unrelated to lung cancer.

Discussion

The tar yield of current cigarettes was unassociated with lung cancer in this study. Other studies which

Table 4. Relative risk (RR) and 95% confidence interval (CI) of lung cancer associated with duration of filtered cigarette use in current smokers with a history of at least 20 years of smoking (12,038 observations; 166 cases)

Duration of filtered cigarette use (years)	Men			Women		
	No. cases	RR[a]	(CI)	No. cases	RR[a]	(CI)
0 (reference)	16	1.0		10	1.0	
1-9	7	0.72	(0.30-1.75)	10	1.08	(0.45-2.59)
10-19	27	0.93	(0.50-1.75)	22	0.70	(0.33-1.49)
≥ 20	43	1.04	(0.58-1.87)	31	0.36	(0.18-0.75)

[a] Adjusted for age, race, education, cigarettes/day, and number of years of smoking.

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Table 5. Cohort and case-control studies regarding the relationship of cigarette tar yield or of filtered cigarette use to lung cancer[a]

Author	(Ref#)	Cohort studies				
		Location of study	Size of cohort	Length of follow-up	No. of lung cancers	Results
Hammond	(1)	USA	458,573 men 593,665 women	2 6-year follow-up periods	839 "adjusted" deaths in smokers	Mortality ratios for lung cancer in smokers associated with low yield cigarettes (< 1.2 mg nicotine, < 17.6 mg tar [with rare exception for tar cutoff]) relative to high yield cigarettes (≥ 2.0 mg nicotine, ≥ 25.8 mg tar) during two 6-year follow-up periods were 0.83 and 0.79 for men, and 0.57 and 0.62 for women. Mortality ratios for lung cancers in smokers associated with intermediate yield cigarettes relative to high yield cigarettes were 0.96 and 0.94 for men, and 0.86 and 0.73 for women
Stellman	(2)	USA	222,830 White men	6 years	969	Standardized mortality ratio (SMR) for lung cancer in smokers associated with low tar cigarette (≤ 17.6 mg) use was 32% lower than the SMR associated with high tar cigarette (≥ 25.7 mg) use
Garfinkel	(3)	USA	619,925 women	4 years	1,006	A 5 mg increase in cigarette tar yield was associated with a 17% increase in risk of lung cancer mortality in current smokers. The standardized mortality for women who smoked filters for 40% of their smoking lifetime or less was 1.51 (1. 29, 1.75) compared with women who smoked filter cigarettes only, among current smokers who had smoked for at least 20 years
Higgenbottom	(4)	UK	17,475 men	10 years	193	Mortality rate for lung cancer associated with tar yield ≥ 33 mg/cigarette was compared with that of smokers of cigarettes with 18-23 mg tar. Results were inconsistent across categories of cigarettes smoked per day
Hawthorne	(5)	Scotland	11,295 men	2-12 years	104	Risk of lung cancer in male current smokers was 17% lower (not statistically significant) in those who normally smoked filtered cigarettes relative to those who normally smoked plain cigarettes
Rimington	(6)	England	10,414 men	69-81 months	104	Risk of lung cancer associated with filter cigarette use relative to non-filter cigarette use was 0.65

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Table 5. *Continued*

Author	(Ref#)	Case-control studies			
		Location of study	No. of cases	No. and type of controls	Results
Lubin	(7)	Western Europe	6,920 men 884 women	13,460 men 1,747 women hospital-based	Risk of lung cancer associated with lifetime filter cigarettes relative to lifetime nonfilter cigarette use was 1.7 for men and 2.0 for women. Non-graded increased risk of lung cancer with increased tar
Wilcox	(8)	New Jersey (USA)	727 men	671 men population-based	Risk of lung cancer associated with tar yield ≤ 14 mg/cigarettes relative to tar yield 21.1-28 mg/cigarettes was 0.6 (95% confidence interval 0.3, 1.1)
Kaufman	(9)	USA and Canada	534 men 347 women	998 men 1,572 women hospital-based	Risk of lung cancer associated with tar yield ≥ 29 mg/cigarette relative to tar yield < 22 mg/cigarette was 4.0 (1.2, 13) for men and 4.7 (1.1, 21) for women for cigarettes smoked at least 10 years before admission
Bross	(10)	Buffalo, NY (USA)	974 White men	974 White men hospital-based	Risk of lung cancer associated with current use of filtered cigarettes relative to use of regular cigarettes was 0.59 (crude); risk associated with filtered cigarette use was generally lower relative to regular cigarette use in 9 different strata of duration and frequency of use
Dean	(11)	England	616 men 150 women	2,563 men 2,958 women population-based	Risk of lung cancer deaths associated with use of mainly filtered cigarettes relative to mainly plain cigarettes was 0.41
Wynder	(12)	USA	557 men 127 women	4,835 men 4,712 women hospital-based	Risk of lung cancer associated with cigarette use ≥ 10 years in current nonfilter smokers relative to long-term filter smokers was 1.26 (0.97, 1.64) in men and 1.37 (0.72, 2.60) in women
Benhamou	(13)	France	1,217 men	1,915 men hospital-based	Risk of lung cancer associated with nonfilter cigarette use relative to lifetime filter cigarette use was 1.23 for current and former smokers combined (not statistically significant)
Wynder	(14)	USA	2,087 men 1,012 women	3,951 men 1,892 women hospital-based	Risk in current smokers of ≥ 10 years duration lifetime filter only use relative to nonfilter only use was 0.69 (0.37, 1.27) in men and 0.64 (0.30, 1.35) in women for Kreyberg I lung cancer (squamous cell, large cell, and oat cell) and was 0.87 (0.43, 1.54) in men and 0.96 (0.62, 1.47) in women for Kreyberg II lung cancer (adenocarcinoma, bronchial, and alveolar cell carcinoma)

[a] Results generally are adjusted for age or duration of smoking, and for number of cigarettes smoked per day; in some cases, adjustment is made for other characteristics.

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have examined the relationship of tar yield or filtered cigarette use to lung cancer are summarized in Table 5. The American Cancer Society's (ACS) Cancer Prevention Studies (I and II) and the Whitehall Study are the only other prospective cohort studies of which we are aware that have examined the relationship between tar yield and lung cancer.[1-4] In the Cancer Prevention Study I, low tar (≤ 17.6 mg) cigarettes were associated with lower mortality from lung cancer than medium (17.7-25.6 mg) and high tar (> 25.6 mg) cigarettes.[1,2] Lung cancer risk in women increased about +0 percent with a doubling of tar yield in the ACS Cancer Prevention Study II, in which nearly all cigarettes smoked by women had tar yields ≤ 20.2 mg.[3] In the Whitehall Study, tar yield was associated with lung cancer mortality in smokers of less than one pack per day who inhaled, and in smokers of one-half pack or more per day who did not inhale.[4] Tar yield was related to lung cancer risk in three case-control studies.[7-9] Studies of the relationship of tar yield to lung cancer have been inconsistent in their controlling for the effects of frequency of smoking.

Possible reasons for the negative findings regarding the relationship of tar yield to lung cancer in this study include compensatory efforts by smokers of low yield cigarettes to increase yield by more vigorous inhalation patterns or by smoking more cigarettes; the latter has been demonstrated previously in this cohort.[23] However, the results were not changed substantially when adjustment for these variables was performed. The inability to assess the long-term tar exposure in our study is a limitation. The tar yield of cigarettes smoked by an individual was likely to have changed over time due to secular trends which have resulted in lower yields from cigarettes in general,[26] and due to brand changes made by the individual. We had available only a relatively late assessment of tar intake. This is an especially important consideration since smoking habits early in life are related strongly to the risk of lung cancer later in life.[27] Another factor which may have an impact on the results of this study is the relatively low level of the cigarette tar yields relative to nearly all the studies reviewed, with the exception of the studies of Garfinkel *et al*[5] and Wilcox *et al*.[8] Lack of statistical power is an unlikely explanation for the negative findings in regard to tar yield, since there was no suggestion of any association between tar content and lung cancer incidence.

The finding of an inverse association between lung cancer risk and filtered cigarette use in women who were long-term smokers is consistent with other cohort[4,5] and case-control[7,12,14] studies. The magnitude of this association is larger in this study than in the other studies. It is likely that the lack of an association between lung cancer risk and filtered cigarette use in men is due to chance. The CI around the estimate of RR associated with the categories of duration of filtered cigarette use was wide and included the estimate of the RR noted in almost all the studies (except for Dean *et al*[14]) which examined the relationship of filtered cigarette use to lung cancer. The results in this and other studies may be biased by unmeasured potential confounders, such as dietary factors and occupational exposures. This study and most other studies of the association of low tar and/or filtered cigarette use with lung cancer have shown more benefit in lowering lung cancer risk associated with the use of filtered cigarettes in women than in men, suggesting the possibility that biologic factors or unmeasured aspects of the smoking habit which differ by gender may influence the impact of filtered cigarette use or of changing tar yield on lung cancer risk.

The association of frequency of inhalation with lung cancer in women is plausible, in that the intake of various components of cigarette smoke depends not only on the number of cigarettes smoked but on patterns of inhalation and puffing. Frequency of inhalation and/or depth of inhalation have been associated with lung cancer in other studies.[37,43] The strength of the relationship of frequency and of duration of smoking to lung cancer are consistent with the findings of other studies, as is the relationship between the length of time since quitting to lung cancer in former smokers.[28]

In summary, there was no association between the tar yield of the currently used cigarette-brand and the risk of lung cancer in this study. Duration of filtered cigarette use in long-term smokers was associated inversely with the risk of lung cancer in women, but not in men. It is important to place this finding in the context that smoking any kind of tobacco cigarette is strongly related to lung cancer, and that frequency and duration of cigarette smoking are more important risk factors for lung cancer than differences in the physical characteristics and biochemical composition of cigarette brands.

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